Decarboxylative Transformations: Synthetic Applications and Mechanistic Investigations

Submitted in partial fulfilment of the requirements of the Degree of Doctor of Philosophy

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"…but Alice had got so much into the way of expecting nothing but out-of-the-way things to happen, that it seemed quite dull and stupid for life to go on in the common way.

Lewis Carroll
Alice's Adventures in Wonderland

Declaration

I, Rachel Grainger, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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Details of collaboration and publications:

1. Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. 'Selective deuteration of (hetero)aromatic compounds via deutero-decarboxylation of carboxylic acids.' *Org. Biomol. Chem.,* **2012**, *10*, 3172-3174.

2. Grainger, R.; Cornella, J.; Blakemore, D. C.; Larrosa, I.; Campanera, J. M. 'The *ortho*-substituent effect on the Ag-catalysed decarboxylation of benzoic acids.' *Chem. Eur. J.,* **2014**, 20, 16680-16687. (The DFT calculations for this project were carried out by Dr. J. M. Campanera at the Universitat de Barcelona).

Abstract

Carboxylic acids are cheap, shelf-stable reagents readily available from several commercial and biological sources. Recent advances in decarboxylative activation has allowed for the application of these reagents as building-blocks in organic synthesis; presenting viable, green alternatives to traditional organometallic or organohalide reagents. This thesis focuses on the development of novel transition metal catalysed decarboxylations, and investigation into the mechanisms of these, and related transformations.

In the first part of the thesis, an extensive overview of the latest decarboxylative methodologies is presented, with discussion of the mechanistic aspects of different metal-catalysed decarboxylations. This is followed by a mechanistic investigation into the silver-catalysed decarboxylation of benzoic acids. In this system, an *ortho* substituent is required to facilitate decarboxylation. Using DFT, kinetic studies and the Fujita-Nishioka LFER we were able to show that the *ortho*-effect is a combination of electronic and steric effects, contrary to previous reports.

In the second part of the thesis a practical, mild and highly selective protocol for the mono-deuteration of a variety of (hetero)arenes is described. Ag-catalysis was shown to facilitate the deuterodecarboxylation of (hetero)aromatic carboxylic acids in D_2O/DMSO.

The last two parts of this thesis focus on the formation and activation of carbon-fluorine bonds. Organofluorine compounds are of great importance to the agrochemical and pharmaceutical industries; however, there are limited examples of selective C-F bond formation that do not require stoichiometric metals, harsh conditions or toxic reagents. Using transition metal catalysis, we investigated a fluorodecarboxylation methodology. Initially this was explored in aromatic systems; though no synthetically useful yields were realised. However, aliphatic carboxylic acids were successfully transformed under aqueous conditions. The developed protocol was exploited to access benzylic fluorides. Subsequently, we established unprecedented metal-free conditions to activate their C-F bonds towards nucleophilic displacement; presenting a novel, decarboxylative methodology to furnish carbon-carbon and carbon-heteroatom bonds.

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Acknowledgements

I would like to express my gratitude to my PhD supervisor, Prof. Igor Larrosa. It has been a really fantastic opportunity to carry out my PhD research under your supervision. I have been able to work on a vast array of really interesting and challenging projects, gained excellent training and I feel that I have grown both as a research scientist and as a person, and for that I am truly grateful.

During my time at Queen Mary, I have met some really great people, including researchers, support staff and students and everyone has made it a fun place to be. I am indebted to all members of the Larrosa group, past and present. You have made my time in the group really enjoyable, not least through research/random discussions over coffee, pompelmatas, strawberry Ribenas and more often then not, beers. We have all had some really great times together and I truly feel that I have made friends for life. Thanks for all the laughs and stay in touch!

To my Mum and Dad, thanks for the genes (obvs!), but above all thank you for encouraging me to take whatever path I felt in life with constant support and love, and always without judgement. To my little Sissy (har har!), on your Top Trumps card your special power would be…'*knows exactly the right time to send cat pictures.'* XxX

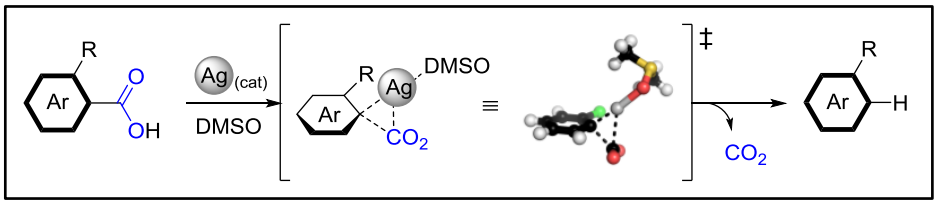
Matt, thank you for well…everything…you always encourage and inspire me; and not least you always take a genuine interest in my work. Here's to the next chapter…

Abbreviations

Ar	Aryl substituent
BDE	Bond dissociation energy
BDTBPMB	1,2-bis-(di-tert-butylphosphinomethyl)benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BPhen	Bathophenanthroline
BSA	Bis(trimethylsilyl)acetamide
Bu	butyl
COD	1,5-Cyclooctadiene
Cy	Cyclohexane (also cyclohexyl)
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4 bis(diphenylphosphino)butane
DMA	Dimethylacetamide
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DMG	Directing Metallation Group
DMSO	Dimethyl sulfoxide
E1	Elimination Unimolecular
E1cB	Elimination Unimolecular conjugate Base
ee	Enantiomeric excess
equiv	Equivalents
Et	ethyl
i	Isomeric branching (also iso)
IPA	Isopropyl alcohol
IR	Infrared Spectroscopy
KIE	Kinetic isotope effect
L	Ligand (specifically a neutral ligand)
LFER	Linear Free Energy Relationship
Me	Methyl
MeCN	Acetonitrile (also CH_3CN)
mp	Melting Point
MS	Molecular sieves
m/z	Mass-to-charge ratio
n	Straight chain
NDHPI	*N,N*-dihydroxypyromellitimide
NHC	*N*-Heterocyclic Carbene
NMP	*N*-methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
OAc	Acetate
OMs	Methanesulfonyl (also mesylate)
OTf	Trifluoromethanesulfonate (also triflate)
OTs	4-toluenesulfonyl (also tosylate)
phen	Phenanthroline
PFA	Perfluoroalkoxy

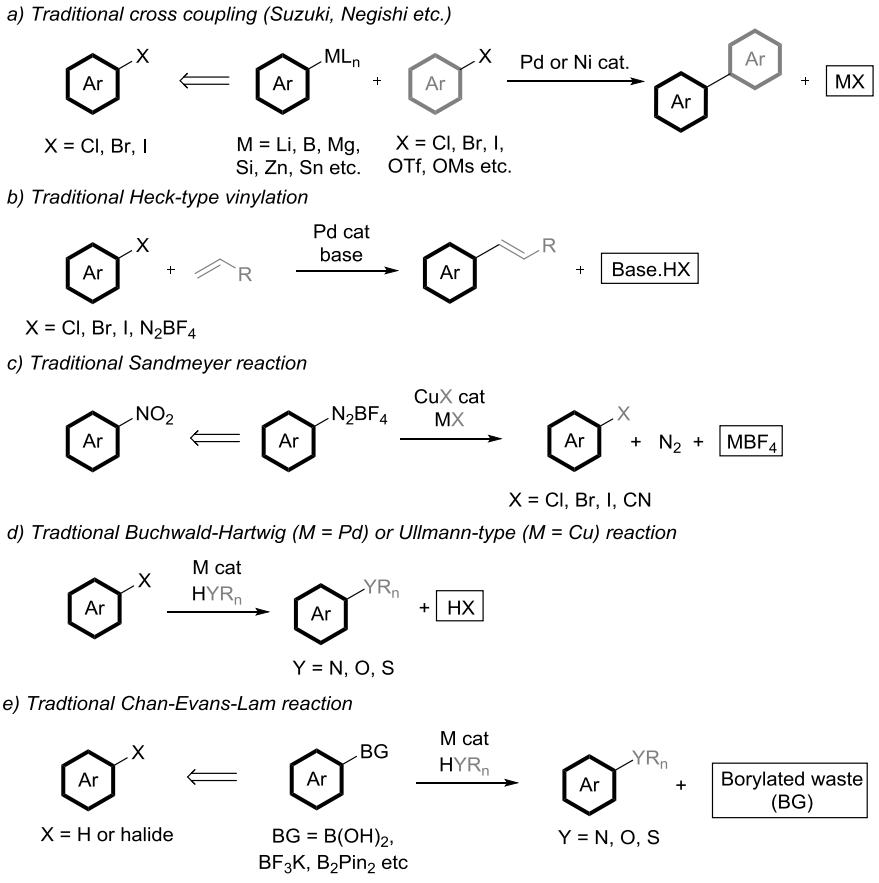
PIDA	Phenyliodonium acetate
pK_a	Logarithmic acid dissociation constant
Pr	Propyl
R	Generic descriptor for an alkyl group or substituent with carbon as the bonding atom
RBF	Round Bottomed Flask
RCY	Radiochemical Yield
RT	Room Temperature
SET	Single electron transfer
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene
SIPr	1,3-Bis(2,6-di-i-propylphenyl)imidazolidin-2-ylidene
SN1	Nucleophilic Substitution Unimolecular
SN2	Nucleophilic Substitution Biomolecular
t	Tertiary branching (also tert)
t	Time
T	Temperature
terpy	2,2';6',2"-terpyridine
TFA	Trifluoroacetate (or trifluoroacetic acid)
TFE	2,2,2-trifluoroethanol
TMAC	Tetramethylammonium chloride
TS	Transition State
X	Halide or pseudohalide (or anionic ligand)
Y	Generic descriptor a substituent with a non-carbon (heteroatom) as the bonding atom

Chapter 1 – The *ortho*-Substituent Effect on the Ag-Catalysed Decarboxylation of Benzoic Acids



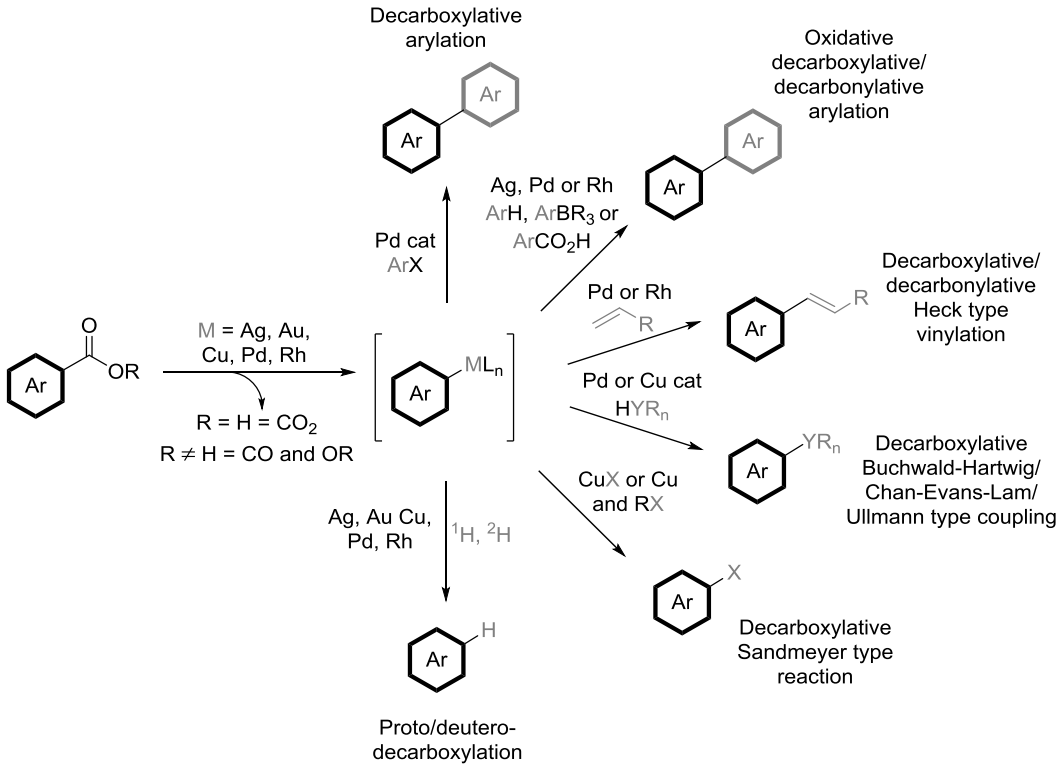
1.1. INTRODUCTION

Transition metal catalysed cross–couplings involve the reaction between two different coupling partners to form a new carbon-carbon or carbon-heteroatom bond linkage. These reactions are achieved by employing a transition metal complex or salt to mediate the activation and connection of the coupling partners; typical metals used to catalyse these processes are copper (Cu), nickel (Ni) and palladium (Pd). Transition metal catalysed cross-couplings have found wide ranging applications in the construction of motifs relevant to the pharmaceutical and agrochemical industries in addition to the synthesis of natural products and functionalised materials. As a result of to the widespread impact of this field, the 2010 Nobel Prize in Chemistry was awarded to Heck, Negishi and Suzuki for their contributions on "palladium-catalysed cross-couplings in organic synthesis".



Scheme 1. General examples of traditional transition metal catalysed reactions including the associated waste generated.

Despite the importance of traditional cross-couplings for the formation of biaryls or functionalised (hetero)arenes, these methodologies do suffer drawbacks, namely the required pre-activation of the aryl coupling partner(s) prior to use (Scheme 1). This prefunctionalisation commonly involves the use of halogenated starting materials or the prior synthesis of diazonium salts (e.g. Sandmeyer reaction) or organometallic species such as boronic acids (e.g. Suzuki reaction). The limitations of these traditional approaches include the expense and sometimes limited shelf life of substrates. When these reagents are not commercially available or the functionalisation is required at a later stage in a multi-step synthesis, cautious handling is required due to the reactive nature of the species generated and reagents used which can limit functional group tolerance and create additional metal and/or halogen-containing waste (Scheme 1).



Scheme 2. General scheme of alternative approaches to traditional cross-coupling utilising transition metal catalysed activation of (hetero)aromatic carboxylic acid derivatives.

In the last decade, a number of alternative methodologies have been developed which employ carboxylic acids as partners in cross coupling reaction. Carboxylic acids are cheap, shelf-stable reagents which are readily available from a variety of commercial and biological sources. Recent advances in decarboxylative activation have exploited the ability of certain transition metals to activate aryl carboxylates towards CO, or more commonly CO_2 extrusion. This in turn generates organometallic aryl donor species which can be functionalised *in situ* (Scheme 2). This approach presents a viable green alternative to traditional organometallic or organohalide reagents in organic

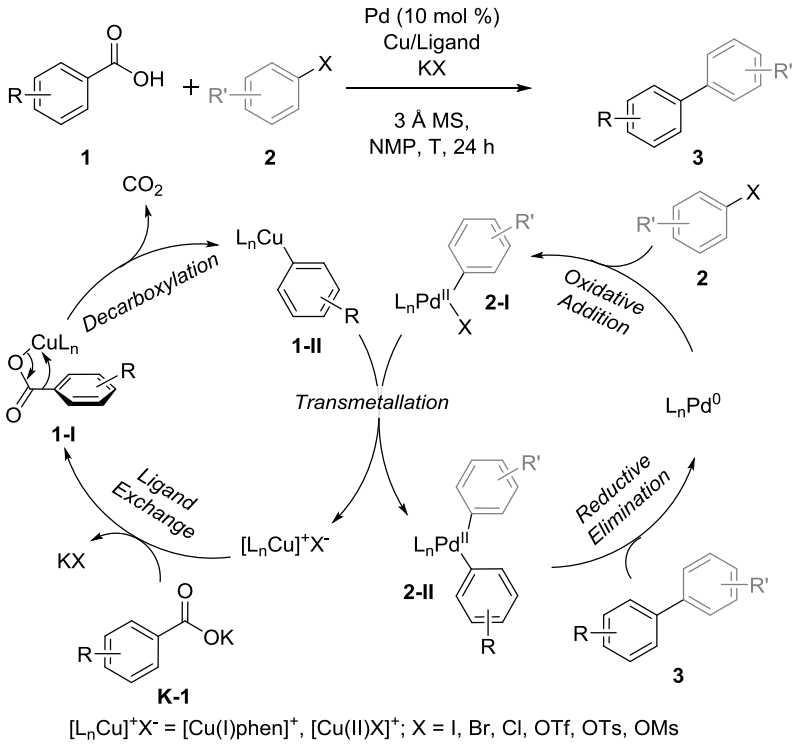
synthesis. Consequently, the main advantages of these approaches are the reduction or complete exclusion of metallic and halogenated waste whilst improving the atom economy of the transformation. Moreover, different transition metals have the propensity to activate different arenes depending on electronic (and sometimes steric) character, so that bimetallic catalytic cycles can work in tandem to activate two (hetero)aryl carboxylic acids (or one acid and one arene through C–H activation), or different reactive pathways can be accessed subsequently with one metal catalyst.

A vast array of decarboxylative and decarbonylative transformations of aromatic and aliphatic acids have now been reported. Excellent reviews by Gooßen[1], Larrosa[2] and Liu[3] discuss a number of the transformations of (hetero)aromatic acids. The focus of this chapter is to give greater insight into the observed '*ortho*-effect' in the Ag-catalysed decarboxylation of benzoic acids and accordingly the preface to this work will focus on the variety of decarboxylative transformations that can be carried out in aromatic systems by different metals (outlined in Scheme 2), with particular attention paid to the mechanistic aspects affecting decarboxylation by different metals.

1.2.1. – Copper-mediated decarboxylative activation

The ability of copper salts to activate benzoic acids towards decarboxylation was first reported in 1930 by Shepard[4] with further work in the field subsequently carried out by Nilsson,[5] Cohen[6] and Sheppard[7] in the 1960s and 1970s. Within these reports stoichiometric amounts of copper were required to form the carboxylates prior to pyrolysis. The intermediacy of aryl-Cu species was demonstrated by Nilsson on the addition of excess iodobenzene and subsequent isolation of the arylated product, including a number of byproducts including the protodemetallated arene.

In 2006, Gooßen and co-workers demonstrated that a bimetallic Pd/Cu system can operate for the decarboxylative cross-coupling of a variety of (hetero)aromatic carboxylic acids and aryl bromides (Scheme 3).[8] Both metals are thought to act independently in two tandem catalytic cycles. The Pd participates in the archetypical Pd(0)/Pd(II) catalytic cycle commonly encountered in traditional cross-couplings. The aryl-Cu species **1-II** is formed via decarboxylative activation of the carboxylate **K-1**. Subsequent transmetallation of **1-II** with **2-I**, regenerates the Cu catalyst by forming a Pd(II) species with two different aryl groups (**2-II**) which can reductively eliminate to form the biaryl product **3** and regenerate the Pd catalyst.



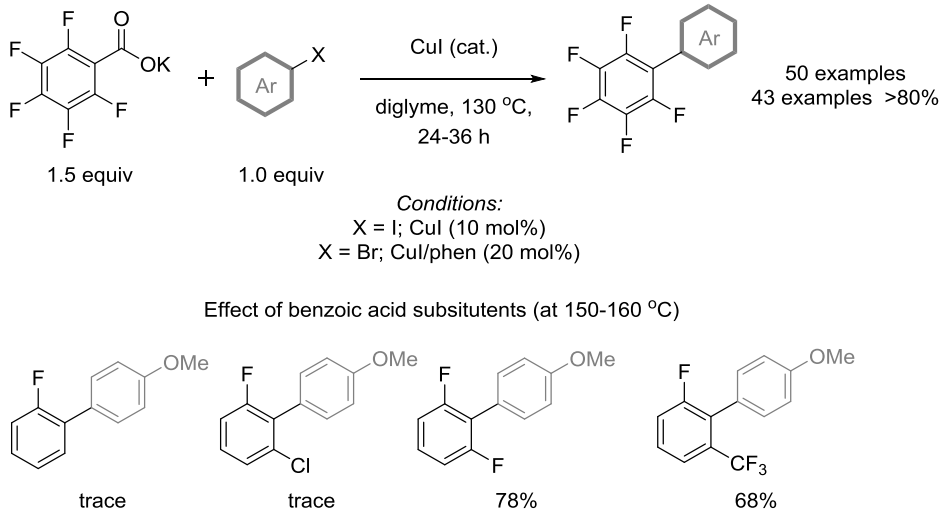
Scheme 3. The bimetallic Cu/Pd catalysed decarboxylative cross-coupling reported by Gooßen *et al.* involves two catalytic cycles working in tandem.[8]

Unlike traditional cross-coupling methodologies which necessitate pre-formation of the aryl-metal species required for transmetallation; the decarboxylative route reduces the overall environmental impact of biaryl formation by reducing the number of synthetic steps required in addition to the amount of metallic waste generated as the organometallic reagent is synthesised in situ and the copper catalyst can be regenerated after transmetallation to Pd. Unfortunately, this methodology requires high reaction temperatures (160 ^{o}C) to promote decarboxylation using substoichiometric amounts of Cu. Nonetheless, the reaction temperature could be lowered to 120 ^{o}C if excess copper salts were used. The initial work by Gooßen utilised aryl bromides as the coupling partner and employed a simple ligand systems which could also be utilised for the cross-coupling of aryl iodides.[8,9] The scope of the aryl electrophile has since been diversified through the development of electron-rich and bulky phosphine ligands for the Pd, permitting arylation with aryl chlorides[10], triflates[11], tosylates[12] and mesylates[13].

1.2.3. – Applications of the Cu-catalysed decarboxylation

The utility of decarboxylative activation by Cu to generate organometallic aryl nucleophiles *in situ* is not limited to Pd catalysed cross-coupling with aryl halides and pseudo halides and has shown application in a number of transformations as outlined in Scheme 2 and discussed below.

In 2009, Liu and co-workers reported that Cu could be employed as the sole catalyst in a decarboxylative cross-coupling of poly-fluorinated carboxylates and aryl bromides/iodides (Scheme 4).[14] The copper can activate both coupling partners by catalysing the decarboxylation and cross-coupling steps in cooperation. The mono-metallic reaction proceeds at lower temperatures than the Cu/Pd bimetallic system reported by Gooßen *et al.* due to the use of electron-deficient poly-fluorinated arenes which are more activated towards decarboxylation with Cu. Accordingly, only trace conversion was observed with 2-fluoro and 2-chloro-6-fluoro benzoic acids, however the more electron-deficient 2,6-difluoro and 2-trifluoromethyl-6-fluoro benzoic acids could be successfully arylated with aryl iodides, albeit at elevated temperatures (150−160 °C).



Scheme 4. Copper catalysed decarboxylative cross-coupling of poly-fluorinated potassium carboxylates and aryl bromides/iodides by Liu *et al.*[14]

A bimetallic Cu/Pd decarboxylative Buchwald-Hartwig type thioetherification was reported by Li *et al.* in 2009.[15] The coupling of a number of aromatic acids bearing electron-withdrawing substituents in the 2 or 4 positions was achieved; further examples of acids bearing *α*-heteroatoms and cinnamic acid were disclosed and the thioetherification could be carried out with a number of aliphatic or aromatic thiols and disulfides (Scheme 5)

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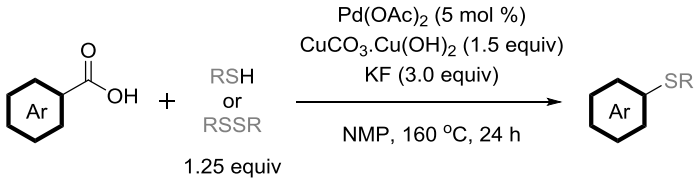
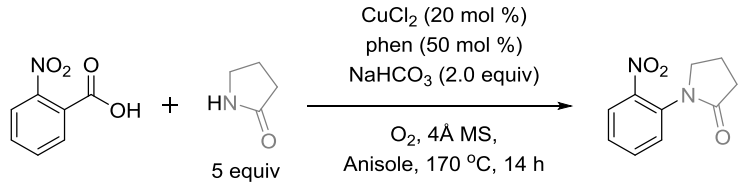


Scheme 5. Cu/Pd catalysed decarboxylative thioetherification of (hetero)aromatic benzoic acids.[15]

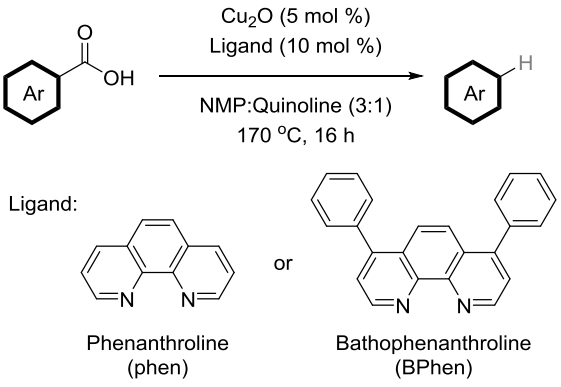
A further example of decarboxylative C-Het bond formation was recently reported by Patel and Mainolfi (Scheme 6).[16] Utilising a monometallic Cu catalytic system, the decarboxylative *N*-arylation of a number of *ortho*-nitro benzoic acids was reported in the synthesis of aromatic amides and sulfonamides. Other examples of acids tolerated in the reaction include benzoates bearing an *ortho* ester, acetophenone, methylsulfone and nitrogenous heterocycles such as 2-pyridines and 1,2-pyrazoles.



Scheme 6. Cu catalysed decarboxylative coupling of 2-nitrobenzoic acid and pyrollidinone reported by Patel and Mainolfi.[16]

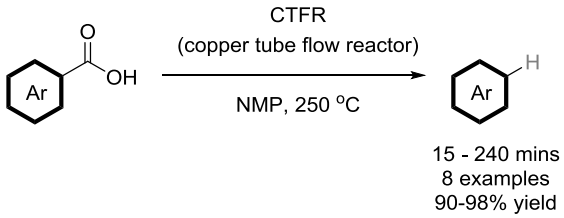
The protodemetallation of aryl-copper intermediates is a common side reaction in Cu-catalysed decarboxylative couplings; to avoid substrate loss through this unconstructive pathway, rigorous exclusion of proton sources from the reaction media is enforced through the use of preformed potassium carboxylates, anhydrous conditions and molecular sieves.

Carboxylic acids can also act as synthetic handles to direct reactivity in aromatic systems either through mesomeric deactivation to promote electrophilic aromatic substitution in *meta* or by chelation to metal centres to direct metallation *ortho* to the carboxyl moiety. Removal of the carboxylic acid group can allow for novel substitution patterns. In 2009 Gooßen reported the first example of copper-catalysed protodecarboxylation using sub-stoichiometric amounts of Cu salts (Scheme 7). The standard Cu/phenanthroline system tolerates a variety of substituents in the *ortho*, *meta* and *para* positions, favouring those which are electron-withdrawing. More challenging substrates such as *p*-methoxy benzoic acid required a modified bathophenanthroline (BPhen) ligand system to achieve good yields (82 % with BPhen cf. 12 % with phen).[17] Furthermore, reaction times can be drastically reduced with the use of microwave heating.[18]



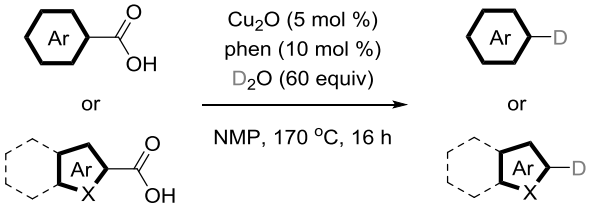
Scheme 7. Cu catalysed protodecarboxylation reported by Gooßen *et al.*[17]

Subsequently, Patel and Manolfi reported the decarboxylation of a number of (hetero)aromatic acids in a flow reactor equipped with copper tubing (Scheme 8). The reaction occurs rapidly at high temperatures. Despite the forcing conditions no reaction is observed using different tubing, thus indicating that the copper tubing is indeed responsible for the reaction, and not solely the elevated temperatures.[19]



Scheme 8. Ligandless Cu catalysed protodecarboxylation in copper tube flow reactor.[19]

Following on from their work on the Cu-catalysed protodecarboxylation of (hetero)aromatic acids, Gooßen *et al.* expanded this methodology towards the selective deuteration of a number of substrates by introducing an excess of deuterons in the form of 60 equiv of D_2O (Scheme 9).[20] Although a good substrate scope is reported the main drawbacks of this methodology (apart from the high temperature, a limitation of all Cu-catalysed decarboxylations) is the comparative lack of operational simplicity. The protocol requires three sequential additions of D_2O over 30 mins while the reaction mixture is stirred under a flow of nitrogen to promote H/D exchange prior to heating. Despite these rigorous precautions to remove proton sources from the system some of their reported deuteration yields are surprisingly low (40-99%).



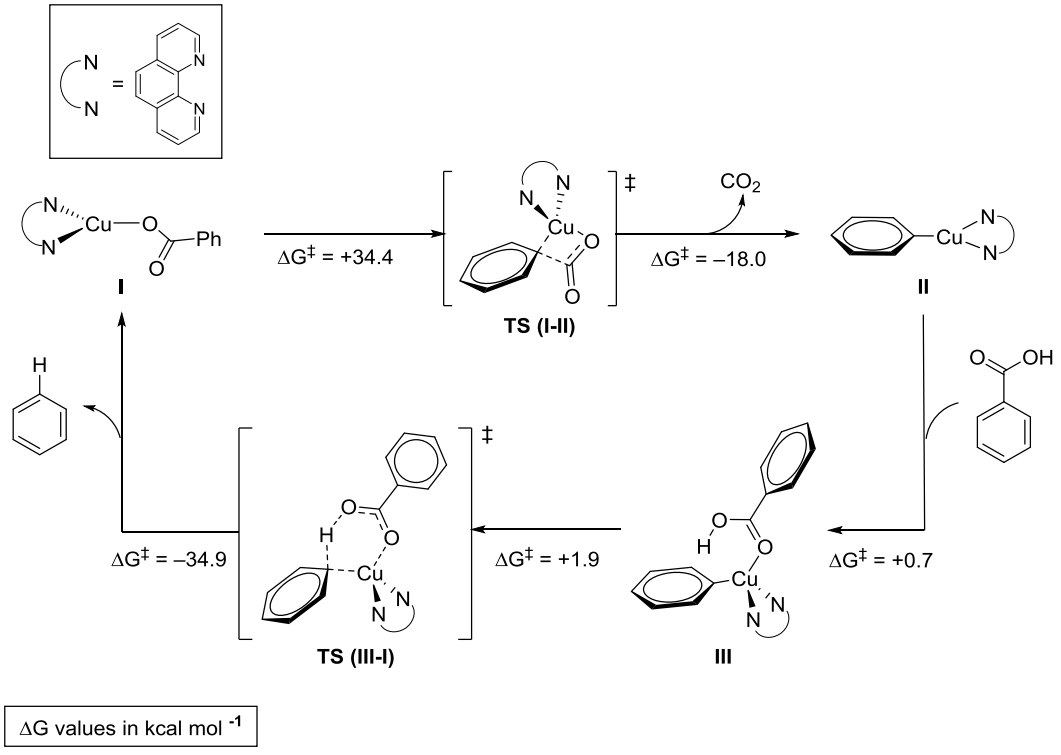
Scheme 9. Cu catalysed deutero-decarboxylation by Gooßen *et al.*[20]

1.2.4. – Mechanistic aspects of the Cu-catalysed decarboxylation

To date, two mechanistic studies on the protodecarboxylation employing the Cu/phen catalyst system have been reported by the groups of Gooßen[21] and a collaborative study by Liu and Su[22]. The important steps in the protodecarboxylation reaction are the decarboxylation step where the aryl carboxylate loses CO_2 and forms an intermediate aryl-copper species, with subsequent protodemetallation of this intermediate and the associated catalyst regeneration.

1.2.4.1. – Decarboxylation event/Protodemetallation

A proposed mechanism for the protodecarboxylation of benzoic acid is shown in Scheme 10. On formation of the catalytically activate complex **I**, the decarboxylation is achieved in one endergonic step involving coordination of Cu centre to the π-system of the arene to form **II** with concomitant extrusion of CO_2 (**I → TS (I-II)** = 34.4 kcal mol^{-1}).[22] Subsequent protodemetallation of the aryl-copper species **II** is highly exergonic involving simultaneous protonation of the arene and catalyst regeneration (**TS (III-I) → I** = −34.9 kcal mol^{-1}). Consequently, the decarboxylation is the rate determining step of the reaction. Substrate loss in decarboxylative transformations frequently occurs through the protodemetallation pathway. This route is energetically favourable and the nucleophilic aryl-copper species is unstable at the high temperatures required to generate it and thus rapidly reacts with errant proton sources in the reaction media.



Scheme 10. Mechanism of the Cu-catalysed protodecarboxylation reported by Liu and Su.[22]

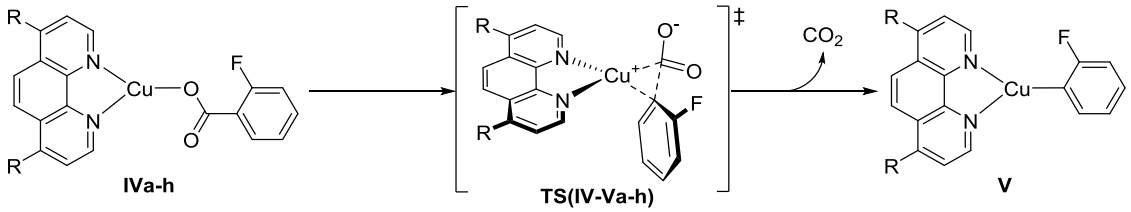
1.2.4.2. – Substrate scope

The copper catalysed decarboxylation is known to tolerate a number of substituents and substitution patterns on the arene; however certain substrates can be challenging. The decarboxylation of alkoxy-substituted arenes is very sluggish with the unsubstituted phenanthroline system, but Gooßen *et al.* have shown that good yields can be achieved with a different ligand

(BPhen, Scheme 7).[17] Nonetheless, some of substrates are completely unreactive with Cu even with the improved ligand system and high reaction temperatures; this includes *ortho*-bromo and -chloro substituted substrates and very electron rich substrates, for example, those with more than one ether substituent.

1.2.4.3. – Effect of ligands

To investigate the ligand effects, Gooßen *et al.* calculated the activation energies for the *ortho* and *para* fluoro copper carboxylates with several different 4,7-di-substituted phenanthroline-type ligands of varying electronic properties.[21] The results obtained with the *ortho*-fluorobenzoate are shown in Figure 1. It was determined that at 170 °C, the decarboxylation is endergonic for all ligands with the electron-rich ligands giving lower barriers to activation for the fluoro substituted acids, with electron-withdrawing substituents having the opposite effect. The reaction rates were calculated using the Eyring equation and it was found that the most electron-rich ligand (R = NMe_2) only gave a 2.5 factor rate enhancement relative to unsubstituted phenanthroline. Unfortunately this beneficial enhancement is offset by the challenging synthesis of this class of ligands. Furthermore, when the ligands were tested in the decarboxylation of *ortho* and *para* nitro benzoic acids the trend observed in the calculations was not fully observed experimentally, presumably due to ligand decomposition.



Substrate	R	$\Delta G^{\ddagger}_{443}$ **IV → TS(IV-V)** (kcal mol^{-1})
IVa	H	31.4
IVb	CN	32.0
IVc	Ph	31.1
IVd	Me	31.2
IVe	SPh	31.6
IVf	OPh	31.9
IVg	OMe	31.1
IVh	NMe_2	30.6

Figure 1. Activation energies for the decarboxylation of copper *ortho*-fluorobenzoates with phenanthroline-type ligands of differing electronic properties.[21]

To corroborate the calculated effects of ligands with differing electronic properties, the protodecarboxylation of *ortho*-nitro benzoic acid was used as a model. Phenanthroline gave 65% conversion in 2 hours with the more electron rich 4,7-dimethyl-1,10-phenanthroline and 4,7-dimethoxy-1,10-phenanthroline giving 75% and 81% conversion, respectively; this indicates that electron-donating substituents on the ligand do indeed improve decarboxylation rate as indicated by the Eyring analysis. Interestingly the 4,7-bis-phenyl substituted bathophenanthroline caused a slight decrease in yield compared to phenanthroline (55%). When the *para* Hammett constant of a phenyl group is considered (σ_p = −0.01) the phenyl groups on C4- and C7-positions of BPhen offer negligible augmentation of the electron density of the ligand, akin to hydrogen; however, they do provide an extension of the π-system and improve the π-backbonding ability of the ligand. Aforementioned, when BPhen was used in the decarboxylation of *para*-methoxy benzoic acid a vast improvement in yield was observed[17] and this points to the importance of the ligand system in the Cu-catalysed decarboxylation of acids with different electronic properties.

As discussed previously, Lin and Su noted that the rate determining decarboxylation step of the Cu/phen system involves conversion of the three-coordinate copper carboxylate **I** to the aryl-copper species **II** (on loss of CO_2), as shown in Scheme 10. This transformation requires rotation of the carboxyl moiety to allow coordination of metal centre to the π-system of the arene through the *ipso* ring carbon to then lose CO_2 in one step **TS(I-II)**. Unlike the Ag-catalysed system (*vide infra*) no intermediate η^2 aryl-copper complex is formed prior to decarboxylation; thus it could be assumed that the electronic nature of the arene and the metal centre are both significant. The nucleophilic ring carbon has to interact with the metal centre, and if it is deactivated by electron-withdrawing groups then increased electron density on the metal centre (through ligand effects) will promote this. Conversely, for electron-rich substituents the increased nucleophilicity of the ring carbon will assist coordination. Of course, the other important process in the decarboxylation step is the lengthening of the C(aryl)−C(COO^-) bond, in the study by Liu and Su *et al.* on the mechanism of the Cu catalysed process it is difficult to accurately determine the effect of a substituent's electronic properties on this bond length in the transition state as all structures for *ortho*-substituted acids have groups which coordinate the metal centre and offer a secondary stabilising effect. However, on comparison of the transition state structures of *meta*-substituted compounds it can be clearly observed that the more electron-withdrawing the substituent the longer the C(aryl)−C(COO^-) bond, similar to the effect in the Pd-catalysed system due to the proposal of an electron-flow mechanism.[23] Whilst electron-rich substrates favour coordination of the aryl π-system to the metal centre, they also disfavour breaking of the C(aryl)−C(COO^-) bond. Accordingly, the improved turnover observed in the Cu-catalysed decarboxylation of electron-rich substrates using BPhen could be attributed to the

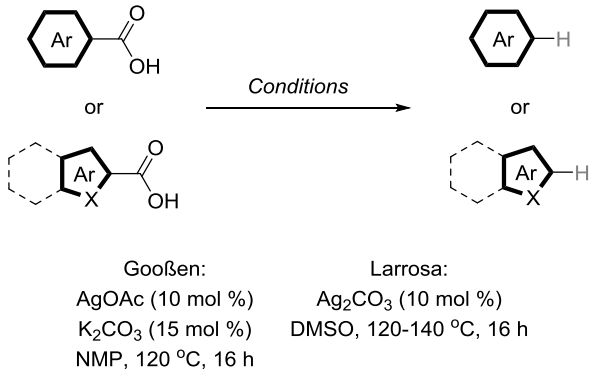
extended π-system assisting removal of electron-density from the arene through π-backbonding after coordination of the metal, thus promoting decarboxylation.

To summarise, copper catalysis can allow access to a variety of new C–C, C–Het and C–H bond formations through copper's ability to activate carboxylic acids towards decarboxylation and also participate in cross-coupling reactions permitting Cu only or Cu/Pd bimetallic catalytic cycles. Cu exhibits a good tolerance to a variety of different substituents on the acid coupling partner; however, the major limitations of these methodologies centre around the high temperatures required (130-240 ^{o}C) to promote decarboxylation in addition to the high polarity, high boiling point solvents which can cause difficult purifications after reactions are complete.

1.3. – SILVER-MEDIATED DECARBOXYLATIVE ACTIVATION

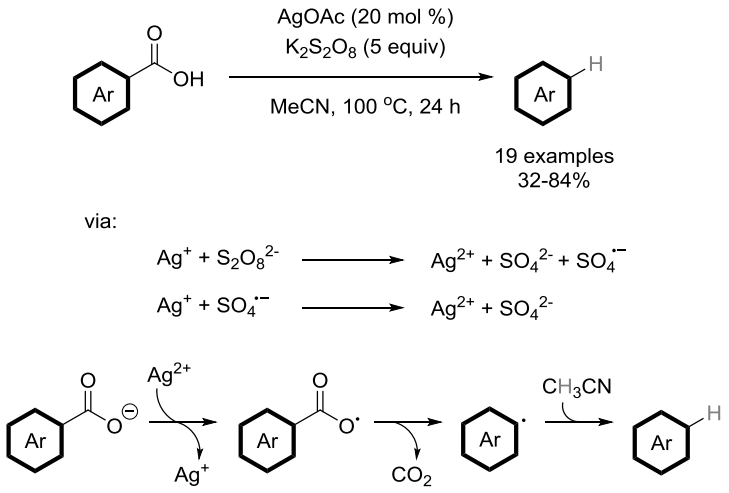
1.3.1. – Discovery

In 1970, whilst working on the protodecarboxylation of nitro-benzoic acids in the presence of copper salts Nilsson discovered that silver salts could also promote decarboxylation at elevated temperature (240 ^{o}C). In 2009, the first examples of Ag-catalysed protodecarboxylation were published contemporaneously by Gooßen[24] and Larrosa[25] (Scheme 11).[26] This work has subsequently been extended to utilise the Ag-catalysed decarboxylative activation for a variety of transformations due to significant advantages over the Cu system, including the development of an analogous deutero-decarboxylation methodology (discussed in Chapter 2).



Scheme 11. Ag-catalysed protodecarboxylation of benzoic acids reported contemporaneously by Gooßen and Larrosa in 2009.[24,25]

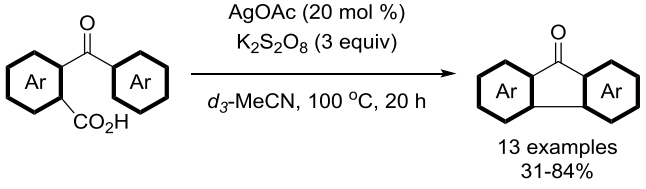
The Ag catalyst system can facilitate the decarboxylation of a greater variety of substituents including electron-rich (excluding OH and NH_2) and electron-deficient substituents compared to the Cu-catalysed system. Furthermore it tolerates halogens other than fluorine (Cl, Br, I) presumably due to the lack of a competing oxidative insertion pathway. The Ag-catalysed route requires significantly lower temperatures with decarboxylations carried out in good yields at 40-50 ^{o}C lower than the Cu system and without the requirement for an exogenous ligand as the preferred reaction solvent DMSO seems to be an excellent ligand for Ag. However, the main drawback in comparison to the Cu-catalysed system is the requirement for an *ortho* substituent on the ring, although it has been demonstrated that the Ag-catalysed decarboxylation of non-*ortho* substituted substrates can occur, but at higher temperatures and in low yields.[17] Like the case of the Cu-catalysed system, the majority of Ag catalysed decarboxylations in aromatic systems occur via a redox neutral pathway, with DMSO as the reaction solvent and ligand for the Ag. However there are notable exceptions to these cases and recently Greaney and co-workers published the first examples of a Ag-catalysed decarboxylation of aromatic acids that occur via a radical pathway (Schemes 12 and 13).[27]



Scheme 12. Ag-catalysed protodecarboxylation of benzoic acids reported by Greaney *et al.* occurs via a radical pathway.[27a]

In the presence of excess peroxydisulfate salts (e.g. $K_2S_2O_8$) Ag(I) sources are oxidised to Ag(II) which facilitates the decarboxylation of a variety of carboxylic acids via a radical pathway (Scheme 12). These conditions were widely exploited by Minisci for the generation and coupling of alkyl radicals.[28] However, application of the oxidative decarboxylation to generate aryl radicals was not reported until 2012, presumably due to the high energetic cost required to generate unstable phenyl radicals. In two closely followed publications, Greaney and co-workers investigated the oxidative decarboxylation for the protodecarboxylation and intramolecular C–H arylation of aromatic acids (Schemes 12 and 13 respectively). They report that decarboxylation can only occur in appreciable yields in nitrile solvents, with acetonitrile giving the highest yields; in the protodecarboxylation methodology, acetonitrile also functions as the hydrogen radical donor (Scheme 12). The intramolecular C–H arylation is carried out in d_3-MeCN to prevent substrate loss through hydrogen abstraction due to the increased strength of the C–D bond (Scheme 13).

Unlike redox-neutral decarboxylations, where the rate of reaction is strongly dependent on the nature of the substituents on the aromatic ring and/or their substitution pattern the Ag(I)/$S_2O_8^{2-}$ route can facilitate the decarboxylation of *ortho*, *meta* and *para* substituted acids, albeit with decreased yields for electron-rich acids.

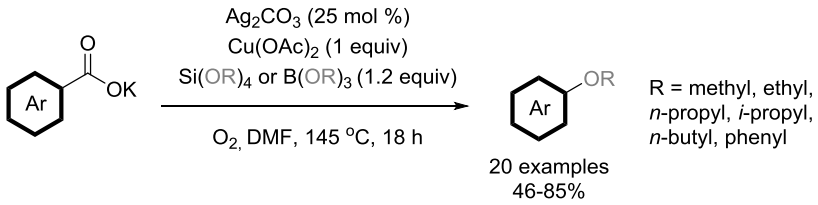


Scheme 13. Ag-catalysed intramolecular arylation of *ortho*-acetophenone benzoic acids reported by Greaney *et al.* occurs via a radical pathway.[27b]

1.3.2. – Applications of the Ag-catalysed decarboxylation

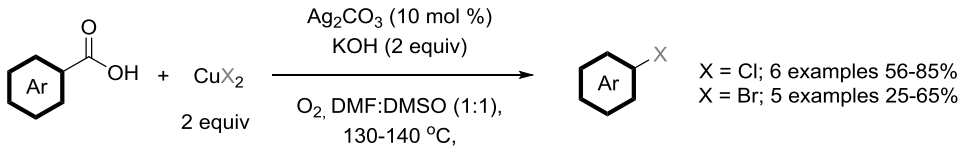
The Ag catalysed decarboxylative activation of (hetero)aromatic acids has been employed in conjunction with Cu and Pd catalysis to effect a variety of bond forming reactions, including state of the art alternatives to classic functionalisations such as the Ullman, Chan-Evans-Lam and Sandmeyer reactions (Schemes 14 and 15) and towards the synthesis of symmetrical and unsymmetrical biaryls (Schemes 16-18) all starting from commercially available benzoic acids or their easily synthesised potassium salts.

Recently, Gooßen and co-workers reported a decarboxylative alternative to an Ullmann/Chan-Evans-Lam reaction employing a Ag/Cu bimetallic system (Scheme 14).[29] Initial studies employing ethanol as the nucleophile resulted in no trace of desired ether product, due to the competing protonolysis of the *in situ* generated aryl metal species. Success was found using silicon and boron alkoxides as the *O*-nucleophile sources and O_2 as the optimal oxidant. This methodology allowed 20 examples of aromatic etherification with alkyl ethers arising from the use of silicon alkoxides and phenoxyethers using triphenylborate as the nucleophile source. Through the isolation of an aryl-silver intermediate they were able to show that copper is required to form the ether product. Furthermore, Ag is required for high yields and high selectivity with a mixture of ether, protodemetallated arene and homocoupled product being observed in its absence.



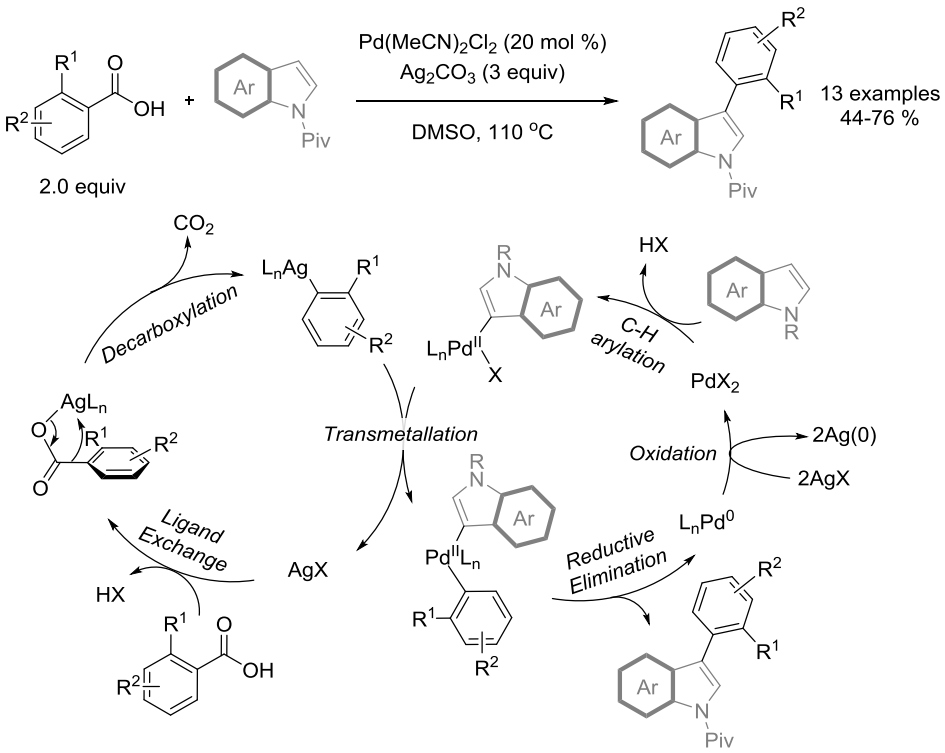
Scheme 14. Ag/Cu-catalysed decarboxylative etherification of benzoic acids reported by Gooßen *et al.*[29]

In 2010, Wu and co-workers reported a decarboxylative Sandmeyer reaction in which benzoic acids were converted into aryl chlorides and bromides using Ag catalysis and copper halide salts (Scheme 15).[30] Despite the utility of the transformation, the substrate scope is limited with some poor yielding examples, moreover the reaction requires an excess of Cu salts with only trace amounts of product observed when catalytic CuX_2 was used in combination with alternative halide salts (e.g. LiCl, TMAC etc).



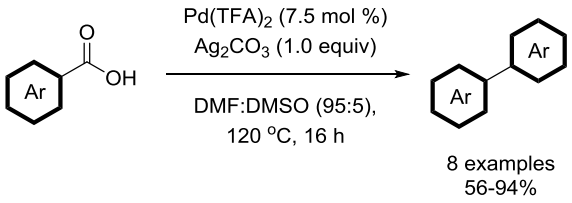
Scheme 15. Ag/Cu catalysed decarboxylative halogenation of benzoic acids reported by Wu *et al.*[30]

In 2009, Larrosa and co-workers reported a procedure for the decarboxylative direct arylation of indoles (Scheme 16).[31] This reaction was the first example of a decarboxylative C−H arylation. The reaction is thought to proceed via two catalytic cycles working in tandem: a Pd-catalysed C−H activation and a Ag−catalysed decarboxylation. The indole undergoes electrophilic palladation at C3 and then transmetallates with the aryl-Ag intermediate formed via decarboxylative activation, subsequent reductive elimination at Pd cross-couples the two arenes forming a new C−C bond and Pd(0) which is then re-oxidised to Pd(II) by excess Ag(I) salts in the reaction media.



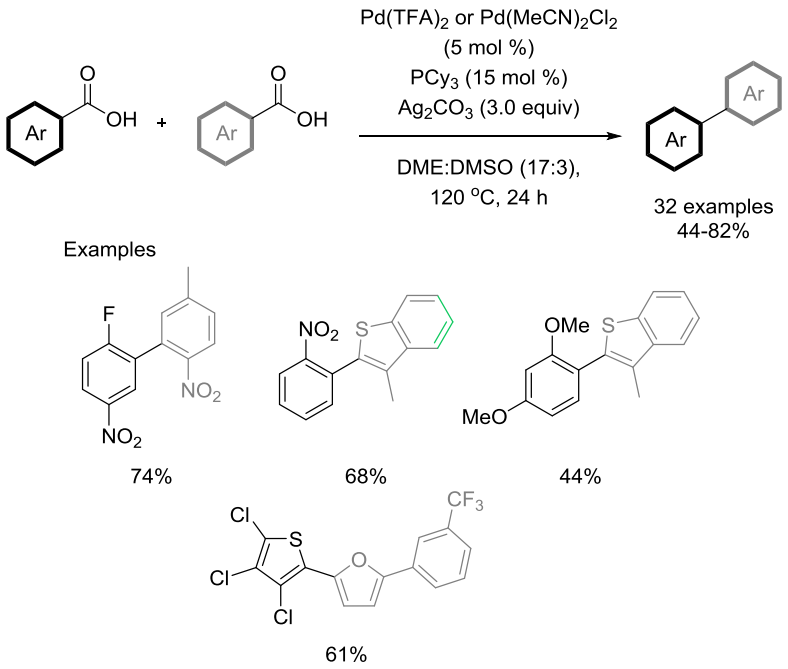
Scheme 16. Pd/Ag catalysed decarboxylative C-H arylation of indoles by Larrosa *et al.*[31]

A side product observed in the direct-arylation of indoles reported by Larrosa *et al.* was the homocoupling of two benzoic acid units; this product arises through a similar tandem Pd/Ag cycle. The reaction conditions were subsequently adapted to capitalise on this reaction, resulting in eight examples of symmetrical biaryls with a number of synthetically useful substituents.[32]



Scheme 17. Pd/Ag catalysed decarboxylative homocoupling of hetero(aromatic) acids by Larrosa *et al.*[32]

A similar dual decarboxylative cross-coupling methodology was also reported by Su *et al.* towards the formation of unsymmetrical biaryls (Scheme 18).[33] By activating two different benzoic acid units either by Pd or Ag decarboxylative activation, several examples of heterocoupled arenes were reported, again with a variety of functional groups.



Scheme 18. Pd/Ag catalysed decarboxylative cross-coupling of hetero(aromatic) acids by Su *et al* for the formation of unsymmetrical biaryls.[33]

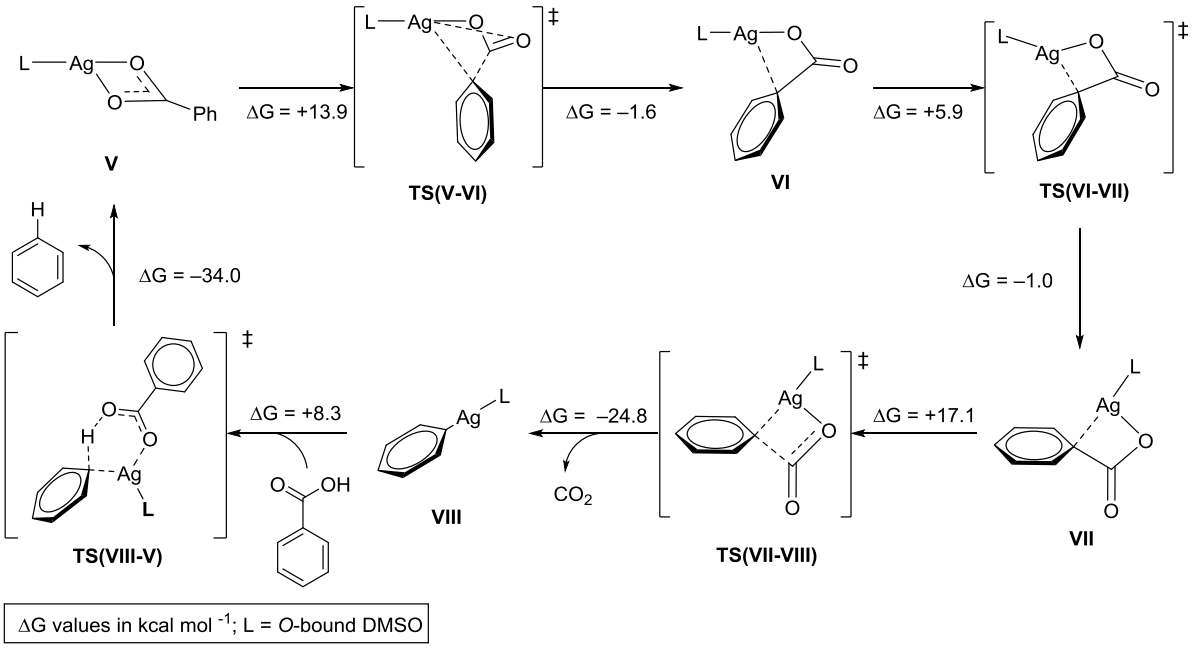
1.3.3. – Mechanistic aspects of the Ag-catalysed decarboxylation

1.3.3.1. – Reduced barrier to decarboxylation compared to copper

In their mechanistic study on the Cu-catalysed decarboxylation (Figure 1), Gooßen *et al.* noted that the barrier to decarboxylation could be dramatically reduced by replacing Cu in the phenanthroline ligated carboxylate complex **IVa** with Ag. Although, phenanthroline is an atypical ligand for Ag, comparison of the activation barriers for the 2-fluorobenzoate complexes reveals that decarboxylation with Ag is exergonic at room temperature ($\Delta_R G_{298}$ = −0.5 kcal mol^{-1}) and more favourable at 120 °C ($\Delta_R G_{393}$ = −3.6 kcal mol^{-1}) than the Cu-catalysed process at 170 °C ($\Delta_R G_{443}$ = −2.8 kcal mol^{-1}).[21]

Lin and Su carried out a detailed mechanistic study on the Ag-catalysed protodecarboxylation and determined that unlike the Cu-catalysed mechanism, the Ag-catalysed process comprises two steps prior to the decarboxylation event.[22] As shown in Scheme 19, these steps involve coordination of Ag to the π-system of the arene forming an η^2 aryl-Ag species (**VI**) with a concomitant isomerisation of

the carboxylate ligand from an $\eta^2 \rightarrow \eta^1$ configuration (ΔG(**V-VI**) = 12.3 kcal mol^{-1}) and then orientation of the metal centre to permit the optimal linear configuration of the ligand–Ag–aryl bond (ΔG(**VI-VII**) 4.9 kcal mol^{-1}). The decarboxylation occurs with concomitant formation and breakage of the aryl–Ag and aryl–carboxylate moieties, respectively (**TSVII-VIII**). The overall isomerisation-decarboxylation process is energetically similar to the Cu-decarboxylation event with a $\Delta G^{‡}$ of 34.3 kcal mol^{-1} (cf. 34.4 kcal mol^{-1}), but the actual metathesis step has a comparatively lower energy requirement of 17.1 kcal mol^{-1}.[22]



Scheme 19. Mechanism of the Ag-catalysed protodecarboxylation reported by Lin and Su.[22]

As previously mentioned, the intermediary η^2 aryl-metal species **VI** (and **VII**) are not observed intermediates in the calculated mechanism of the copper catalysed reaction, this is presumably due to the bidentate phenanthroline ligand preventing the Cu(I) centre from adopting a 4-coordinate configuration.[22,34] This observation was corroborated by Lin and Su on analysis of the phenanthroline-Cu carboxylate complex **I** which prefers to adopt linear 3-coordinate T-shaped geometries rather than 4-coordinate geometries with the other available oxygen atom of the carboxylate. Further studies by Gooßen *et al.* confirmed that no further intermediates could be found which involved π- or η^2- bound aryl-Cu complexes.

1.3.3.2. – Substrate scope

In their 2010 comparative study of the Ag and Cu-catalysed protodecarboxylation of (hetero)aromatic acids, Gooßen and co-workers investigated the scope of both metals using the following reaction conditions: 10 mol % AgOAc in NMP at 120 ^{o}C; and 5 mol % Cu_2O/10 mol % phenanthroline in NMP:quinoline (3:1) at 170 ^{o}C for 16 h.[21] In this work they noted that both catalyst systems tolerated a variety of heteroaromatic acids bearing the carboxylic acid α to the heteroatom, and benzoic acids bearing electron-withdrawing nitro and sulfone groups in the *ortho* position. However, there were also stark contrasts in reactivity for different types of substituents. The Ag-catalysed system can facilitate the decarboxylation of acids bearing *ortho* methoxy, chloro and bromo substituents in good to excellent yields, yet no conversion is observed for these substrates when Cu is used as the catalyst even at 170 ^{o}C. Further examples of the wide substrate tolerance of the Ag-catalysed system can be observed in numerous publications by Larrosa and co-workers.[25,31,32]

1.3.3.3. – Ortho effect

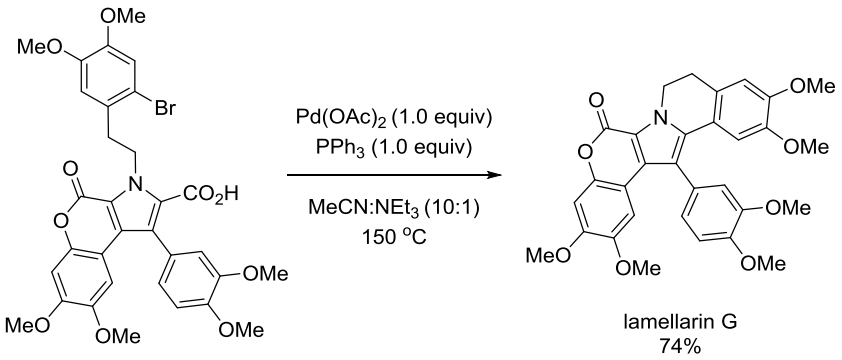
Despite the improved substituent tolerance and lower reaction temperature offered by the Ag-catalyst system (compared to Cu) the main limitation of the protocol is the requirement of a substituent in *ortho* (or heteroatom in α) to promote reactivity. There are limited examples of non-*ortho* substituted benzoic acids showing reactivity with Ag however higher reaction temperatures (160 ^{o}C) are required and the yields are lower than those reported using Cu. Furthermore, these rare examples are limited to *meta* and *para* alkoxy benzoic acids and no reaction is reported with nitro, cyano, acetyl or *N*-acetyl substituents at the 4-position. In contrast to the Cu-catalysed system, these substrates can be decarboxylated in good to excellent yield using bathophenanthroline as the ligand.[21]

Lin and Su first investigated the *ortho*-substituent requirement in the Ag-catalysed system.[22] The transition states for a number of *ortho*-substituted acids were calculated for substituents of varying properties. From these calculated barriers the conclusion could be drawn that an *ortho*-effect does indeed exist with a decreased barrier to decarboxylation observed for the majority of substituents compared to the unsubstituted benzoic acid. Substituents with oxygen atoms able to form 5-membered coordination cycles with the Ag atom (e.g. NO_2, CHO, COMe, $CONMe_2$) helped further decrease the activation threshold by stabilising the transition state. However, Lin and Su noted that there was no clear trend observed between the activation barrier and the electronic properties of the substituent. There is substantial evidence to refute this claim and it will be discussed in detail in the main body of this chapter.

1.4. – PALLADIUM-MEDIATED DECARBOXYLATIVE ACTIVATION

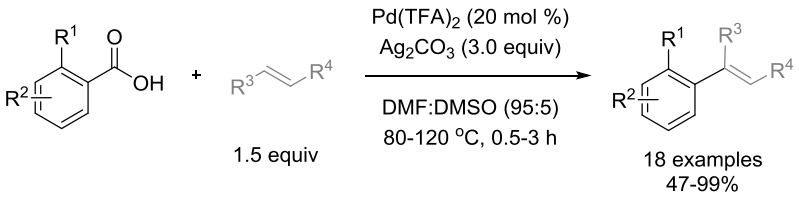
1.4.1. – Discovery

In 1997, Steglich reported the biomimetic synthesis of lamellarin G trimethyl ether, a member of the polycyclic marine pyrrole alkaloids which have shown to be potent anti-proliferative agents. During the synthesis, an intramolecular Pd-catalysed decarboxylative arylation was utilised to complete the polycyclic backbone, and this would become the first example of a Pd-catalysed decarboxylative arylation (Scheme 20).[35]



Scheme 20. Pd decarboxylative intramolecular arylation towards the formation of lamellarin G reported by Steglich *et al.*[35]

Subsequently, in 2002, Myers *et al.* reported the first example of a Pd catalysed decarboxylative coupling using sub-stoichiometric amounts of Pd towards a Mizoroki-Heck-type coupling (Scheme 21).[36] Acids bearing both electron-donating and withdrawing substituents were tolerated. Initial studies carried out with $Pd(TFA)_2$, K_2CO_3 and $Cu(TFA)_2$ were successful for the reaction with 2,4,5-trimethoxybenzoic acid and styrene (82%) however these conditions did not translate well with the less electron-rich acids which were recovered unchanged from the reaction mixture. The use of Ag_2CO_3 (3.0 equivalents) *in lieu* of K_2CO_3 and $Cu(TFA)_2$ improved the efficiency and scope of the reaction with the rationale that Ag_2CO_3 acts as both the base and the stoichiometric oxidant prolonging the lifetime of the active catalyst.

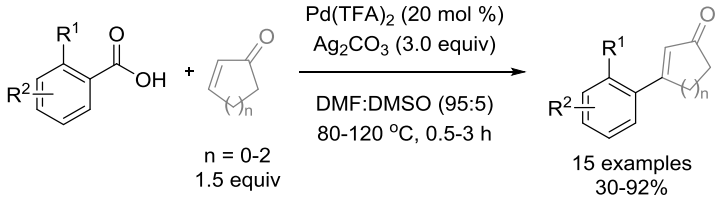


Scheme 21. Pd decarboxylative Heck type coupling reported by Myers *et al.*[36]

1.4.2. – Applications of the Pd-catalysed decarboxylation

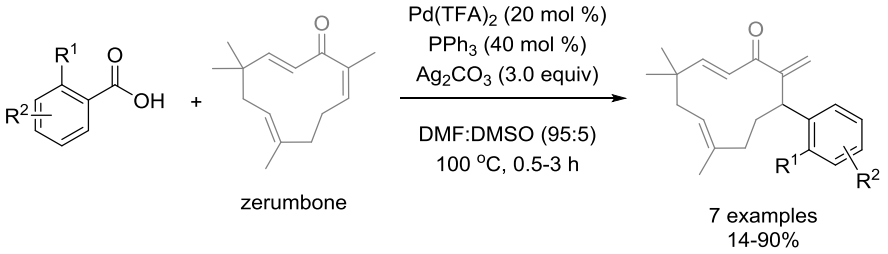
1.4.2.1. – Mizoroki-Heck-type vinylation

Since these initial reports the Pd-catalysed decarboxylation methodology has found a variety of applications. Myers and co-workers showed that their conditions could be easily applied towards the decarboxylative Heck type arylation of cyclic enones, with successful arylation of 5-7 membered substrates in similarly short reaction times (Scheme 22).[37]



Scheme 22. Pd decarboxylative Heck type coupling of cyclic enones reported by Myers *et al.*[37]

Subsequently, Radhakrishnan and co-workers utilised this methodology for the regioselective decarboxylative arylation of novel zerumbone derivatives as a new class of α-glucosidase inhibitors (Scheme 23).[38] The results were poor to fair for a variety of electron-rich benzoic acids, with the electron-poor 2,6-difluoro-4-methoxy benzoic acid being completely unreactive in the reaction conditions. The presented methodology gave rise to a number of zerumbone analogues which showed improved α-glucosidase inhibition compared to unsubstituted zerumbone, and comparable or improved inhibition compared to acarbose.

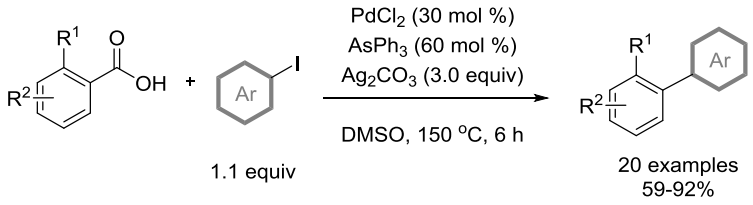


Scheme 23. Synthesis of zerumbone derivative utilising the Pd-catalysed decarboxylative Heck type coupling by Radhakrishnan *et al.*[38]

Despite the utility of the zerumbone derivatives, the majority of the synthetic yields were disappointing, however they could have been improved with exclusion of phosphine ligands. Myers and co-workers explicitly demonstrated in their 2004 study that phosphines had a detrimental effect on both the decarboxylative and traditional Heck vinylations of electron-rich arenes.[37]

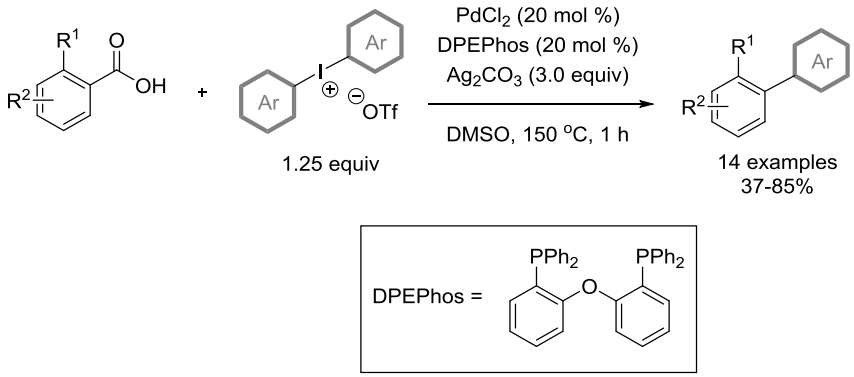
1.4.2.2. – Biaryl Cross-couplings

The Pd-catalysed decarboxylation has also been exploited in a variety of cross-couplings towards the formation of biaryl. In 2007, Becht and co-workers achieved the decarboxylative arylation of aryl iodides in good to excellent yields and short reaction times (Scheme 24).[39] However, the protocol had a limited substrate scope with only fluoro, nitro and alkoxy substituted acids reported, moreover high reaction temperatures were required (150 ^{o}C) in addition to relatively high catalyst loadings (30 mol %) and the use of a toxic arsine ligand.



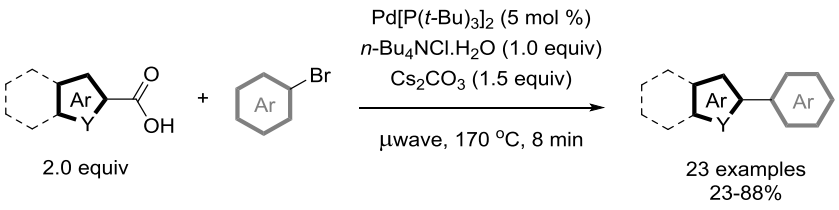
Scheme 24. Pd/Ag catalysed decarboxylative arylation of aryl iodides by Becht *et al.*[39]

Subsequently, an improved methodology was reported by Becht *et al.* utilising bis-aryl iodonium salts as the coupling partners (Scheme 25).[40] This modification allowed for reaction with slightly reduced loading of catalyst (20 mol %) and using a commercially available phosphine ligand (DPEPhos) in a reduced reaction time of 1 h.



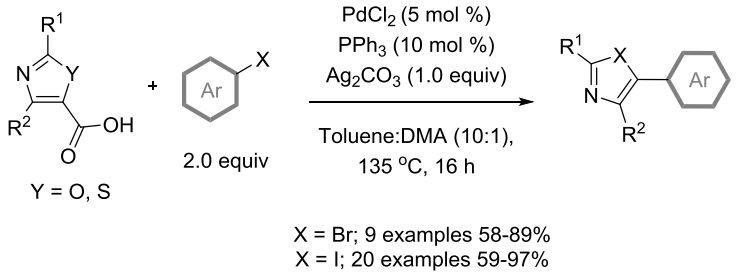
Scheme 25. Pd/Ag catalysed decarboxylative arylation of iodonium salts by Becht *et al.*[40]

In 2006, Bilodeau and Forgione reported the decarboxylative arylation of heterocycles in rapid reaction times using microwave irradiation (Scheme 26).[41] The reaction is thought to occur via electrophilic aromatic substitution of the aryl-Pd(II) species (formed after oxidative addition) onto the C2-position of the heteroarenes followed by extrusion of CO_2 then reductive elimination to form the arylated product.[42]



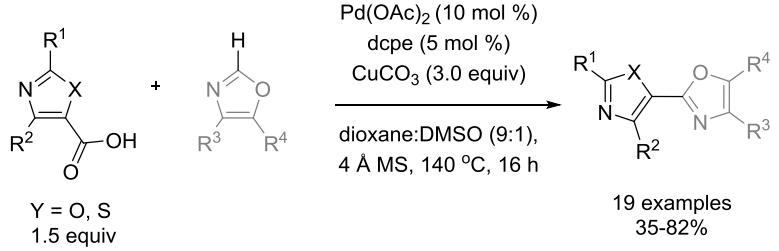
Scheme 26. Bilodeau and Forgione's decarboxylation arylation of heterocycles.[43]

Recently Greaney and co-workers reported the decarboxylative arylation of azoyl carboxylic acids with both aryl bromides and iodides tolerated as the coupling partner (Scheme 27).[43] The reaction requires both Ag and Pd, with no conversion observed when the Ag salts were replaced for Cu salts. It is likely that the Ag source acts as both a base and to sequester halides in the reaction media as it was observed during the optimisation of the reaction with 4-methyl-2-phenylthiazole-5-carboxylic acid and phenyl iodide, that reducing the total loading of silver to 60 mol % resulted in 57% arylation compared to the optimal conditions that yielded 96% product with 1 equiv Ag_2CO_3. The scope of the reaction was investigated with thiazole and oxazole carboxylic acids and tolerates a variety of aryl halides including heteroaryl iodides, such as pyridines, *N*-protected indoles and thiazoles.



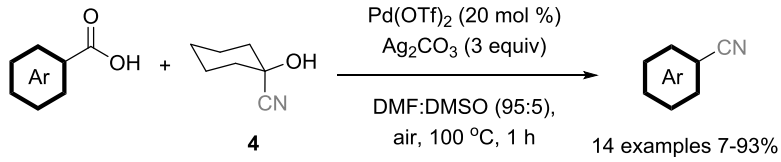
Scheme 27. Pd/Ag catalysed decarboxylative crosscoupling of azoyl carboxylic acids and aryl halides reported by Greaney *et al.*[43]

The application of the decarboxylative activation of azoyl carboxylic acids was expanded by Greaney and co-workers towards the C–H arylation of azoles (Scheme 28).[44] This methodology represents a state of the art adaptation of their initial work to furnish unsymmetrical bis-heteroaryl scaffolds that are important motifs in bioactive natural products, pharmaceuticals and functional materials.



Scheme 28. Pd catalysed decarboxylative C–H arylation of azoles reported by Greaney *et al.*[44]

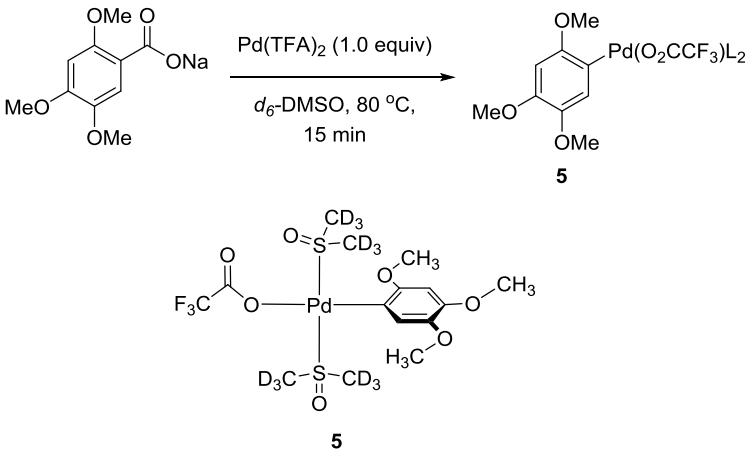
Recently, Taran and co-workers reported the decarboxylative cyanation of a number of (hetero)aryl carboxylic acids (Scheme 29).[45] This procedure represents a modern example of a Sandmeyer-type cyanation which usually involves the reaction of aryl-diazonium salts with CuCN. Accordingly, the procedure reported by Taran *et al.* improves on this traditional methodology by utilising substrates which do not require prefunctionalisation. However cyclohexane cyanohydrin **4** carries the same safety hazards as metal cyanides but with increased economic cost. Furthermore, despite the utility of the transformation the substrate scope suffers from some very low yielding examples.



Scheme 29. Ag/Pd catalysed decarboxylative cyanation of benzoic acids reported by Taran *et al.* using cyanohydrin **5**.[45]

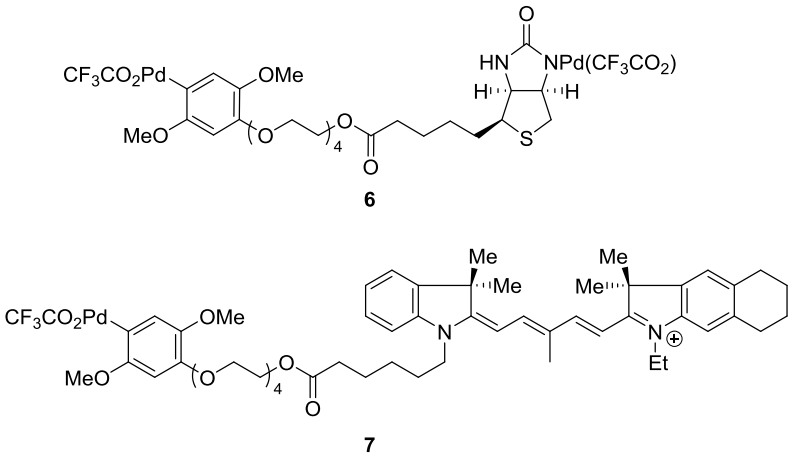
1.4.2.3. – The stability of Aryl-Pd complexes

Following their original reports on the Pd-catalysed decarboxylative Mizoroki-Heck-type vinylations, Myers and co-workers reported a detailed mechanistic study of the reaction using 2,4,5-trimethoxybenzoic acid as the model substrate.[46] The authors reported the isolation and structural (X-Ray) characterisation of a stable palladated intermediate **5** (Scheme 30). This stable complex performed differently in the vinylation, compared to palladated species accessed through traditional Heck route (from aryl iodides) with species **5** preferentially reacting with electron-rich olefins. This indicates that these intermediates are electron deficient; accordingly **5** is accessed from decarboxylation with $Pd(TFA)_2$ whereas the analogous traditional Heck route involves oxidative addition into Ar-I bond starting from Pd(0).



Scheme 30. Isolation of a stable aryl-Pd(II) complex **5** reported by Myers *et al.*[46]

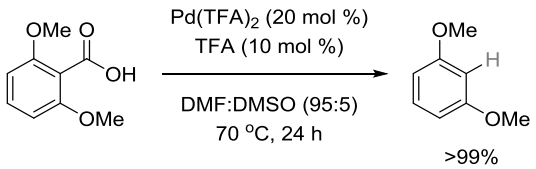
The stability of the Ar-Pd intermediates isolated in the 2005 paper inspired the authors to develop storable ArPd(II) reagents for alkene labelling in aqueous media via Heck type coupling of biotinylated or indocyanine dye coupled aryl-palladium species (Scheme 31).[47] Complexes **6** and **7** were used in the tagging of styryl modified Taxol derivatives and FK-506-based affinity probes.



Scheme 31. Storable aryl-Pd(II) intermediates **6** and **7** developed by Myers *et al.* for the rapid incorporation of a biotin or indocyanine dye tag, respectively.[47]

1.4.2.4. – Protodecarboxylations

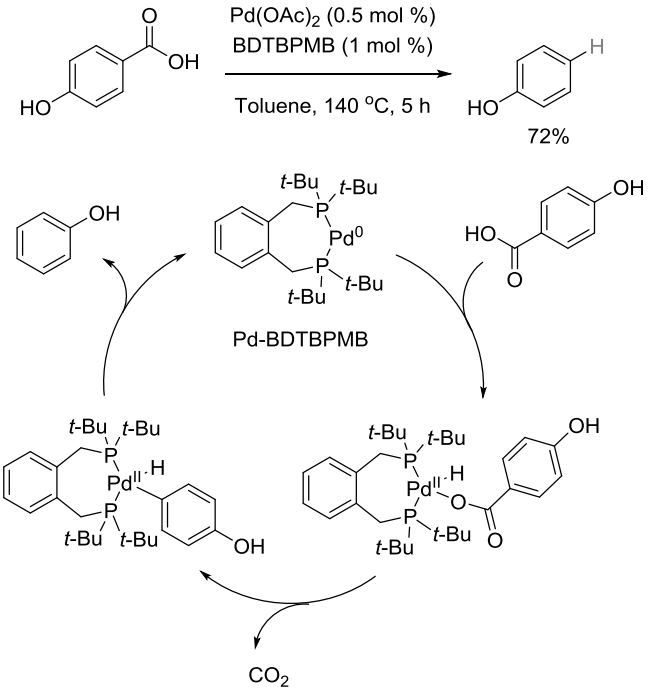
In 2007, Kozlowski *et al.* reported the Pd-catalysed protodecarboxylation of electron-rich alkoxy substituted benzoic acids (Scheme 32).[48] The protocol requires the addition of a catalytic amount of a strong acid to protodemetallate the *in situ* formed aryl-Pd(II) species. Extensive mechanistic studies indicated that for 2,6-dimethoxybenzoic acid the rate of formation of the aryl-Pd species is faster than the protonlysis step, and thus acid is required for protodemetallation and concomitant catalyst regeneration. In this work the authors noted that bis-*ortho* substituted compounds were optimal as the use of mono-substituted compounds suffered from a competing C-H insertion in the position adjacent to the carboxyl moiety.



Scheme 32. Kozlowski *et al.* Pd-meditated protodecarboxylation of electron-rich benzoic acids.[48]

In 2009 Cole-Hamilton and co-workers reported the Pd-catalysed decarboxylation of 4-hydroxybenzoic acid (Scheme 33).[49] The reaction proceeds in good yield with very low loadings of

catalyst. A variety of different phosphine ligands were tested and tri-alkyl phosphines and bidentate phosphines with large bite angles proved the most effective. The requirement for phosphine ligands to afford good yields led the authors to propose a Pd(0)/(II) catalytic cycle, which is different to the reports of Myers[37] and Kozlowski[48] where an electron-deficient Pd(II) centre facilitates a redox neutral decarboxylation. Unfortunately, the reaction seems to be very substrate specific with no conversion observed with benzoic, 3-hydroxybenzoic or 4-methoxybenzoic acid. Interestingly the preferred reaction solvent is toluene, Kozlowski *et al*. also reported that the Pd(II) redox neutral protodecarboxylation can be achieved in good yields in the presence of solvents other than DMSO and DMF, including protic solvents such as MeOH and *i*-PrOH and aromatic solvents such as xylenes at 70 °C.



Scheme 33. Cole-Hamilton *et al.* Pd-mediated protodecarboxylation of 4-hydroxybenzoic acid.[49]

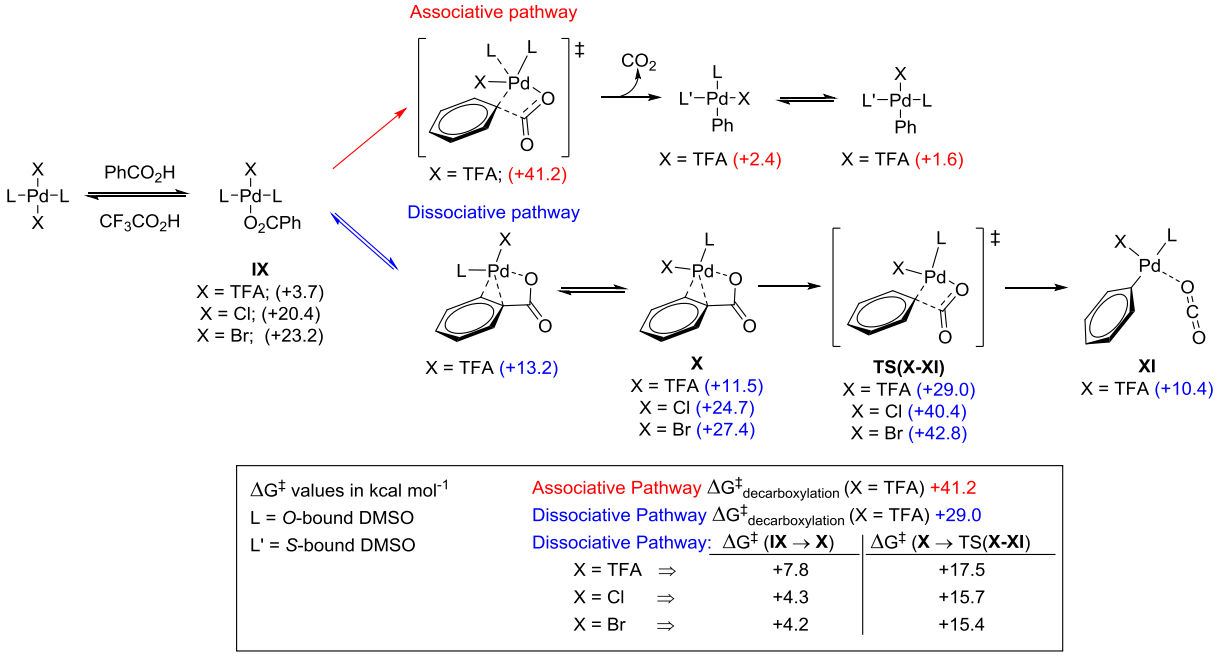
1.4.3. – Mechanistic aspects of the Pd-catalysed decarboxylation

To date, the most widely studied mechanism of Pd-mediated decarboxylation involves the Pd(II) redox neutral system involving electron-rich benzoic acids and an electron-deficient $Pd(TFA)_2$ pre-catalyst and DMSO as the solvent and a source of ancillary ligands.[23,50] This section will focus on all aspects of the decarboxylation and discuss the factors that affect reactivity in this system.

1.4.3.1. – Decarboxylation Event

Following on from Myers' publications on the Pd-catalysed decarboxylative Heck coupling, Liu and co-workers reported a theoretical analysis of the reaction mechanism.[50a] The decarboxylation step

was found to be rate-limiting with a dissociative pathway involving loss of a DMSO ligand from the metal centre before extrusion of CO_2 being favoured in comparison to an associative pathway (Scheme 34). Further analysis of the factors affecting the efficiency of the decarboxylation involved modelling the effect of different anionic and neutral ligands on Pd. Myers and co-workers found that the trifluoroacetate ligand played a key role in promoting decarboxylation with a marked reduction in reactivity with the use of Pd salts with ligands that have a greater trans-influence than trifluoroacetate (e.g. chloride and bromide) with the addition of bromides inhibiting decarboxylation. Through DFT calculations, this observation was rationalised due to the larger energetic cost of the initial carboxylate ligand exchange step despite the stabilising effect of the halides on the transition state.



Scheme 34. Liu *et al.* reported that the Pd-catalysed decarboxylation occurs via a dissociative pathway and that the electron-deficient TFA ligand affords a lower barrier to activation compared to chloride and bromide.[50a]

1.4.3.3. – Effect of ligands

To investigate the effect of ligands, a number of common neutral ligands were modelled, with DMSO giving the lowest activation energy, and phosphines and phosphites giving the highest barrier to activation. This observation can be rationalised due to a combined effect of the σ-donor ability of phosphines/phosphites increasing the electron density of the Pd centre and consequently making CO_2 extrusion more difficult. Furthermore, there is an increased barrier to carboxylate ligand exchange due to a stronger interaction with Pd resulting from a stronger π-acidity compared to DMSO. This energetic consideration corroborates the inferior decarboxylation observed with the

addition of phosphines. Moreover, *N*-heterocyclic carbenes were calculated to be the worst ligands as a result of their electron-rich nature and strong affinity for coordinating Pd. Liu and co-workers also modelled the effect of other group 10 metals such as Ni and Pd for the decarboxylation of benzoic acid but failed to investigate the ability of Ag salts, considering that silver carbonate is used in super-stoichiometric amounts in Myers' protocol.[36,37] As discussed in the previous section, Ag is a competent decarboxylation catalyst particularly in DMSO. As noted in their initial paper, Myers *et al.* mentioned that the reaction of the electron-rich 2,4,5-trimethoxybenzoic acid and styrene proceeded well in the presence of $Pd(TFA)_2$, K_2CO_3 and $Cu(TFA)_2$, yet these conditions had to be modified for electron-deficient substrates by replacing the Cu salt for a source of Ag. Hence, it is likely that Ag_2CO_3 plays a key role other than acting as a base and oxidant, and it is probable that the decarboxylation of electron-deficient substrates in is fact facilitated by Ag and not Pd. Substrates such as 2-NO_2-benzoic acid were reactive in the vinylation reaction despite there being an increased barrier to activation calculated by Liu *et al.* Furthermore, Liu and co-workers reported that there is a linear dependence between increased C_{ipso}-H bond acidity and the barrier to decarboxylation yet 2-nitrobenzoic acid is clearly anomalous. It must be noted that the first examples of catalytic Ag-catalysed decarboxylation were not reported until after Myers' work and thus it is highly understandable that these conclusions were not drawn at the time.

Shortly after Liu's publication, Su and Lin also reported an in depth DFT study modelling the Pd-catalysed decarboxylative Heck reaction reported by Myers *et al.,* with focus paid to the substituent effect on the rate-limiting decarboxylation process. They confirmed that similar to the case of the Ag-catalysed system, *ortho*-substituents reduce the barrier to reaction in comparison to their *meta* and *para* isomers, except in the case of methoxy substituted acids where similar barriers to activation are calculated for all isomers. Furthermore, electron-donating substituents offer a significant reduction in the activation barrier due to a shortening of the C(aryl)–Pd bond and lengthening of the C(aryl)–C(carboxylate) bond. Conversely electron-withdrawing substituents have an opposite effect on these bonds which are key parameters in the decarboxylation.

1.4.3.4. – Protodepalladation and the effect of protic media

In their mechanistic study on the Pd-catalysed protodecarboxylation of electron-rich benzoic acids, Kozlowski and co-workers carried out a thorough investigation of the protodemetallation step.[51] In the Ag and Cu catalysed systems, the protodemetallation step is highly exothermic (34-35 kcal mol^{-1}),[22] however this is not the case for the Pd-system where additional acid is required to promote product formation and hence catalyst turnover.

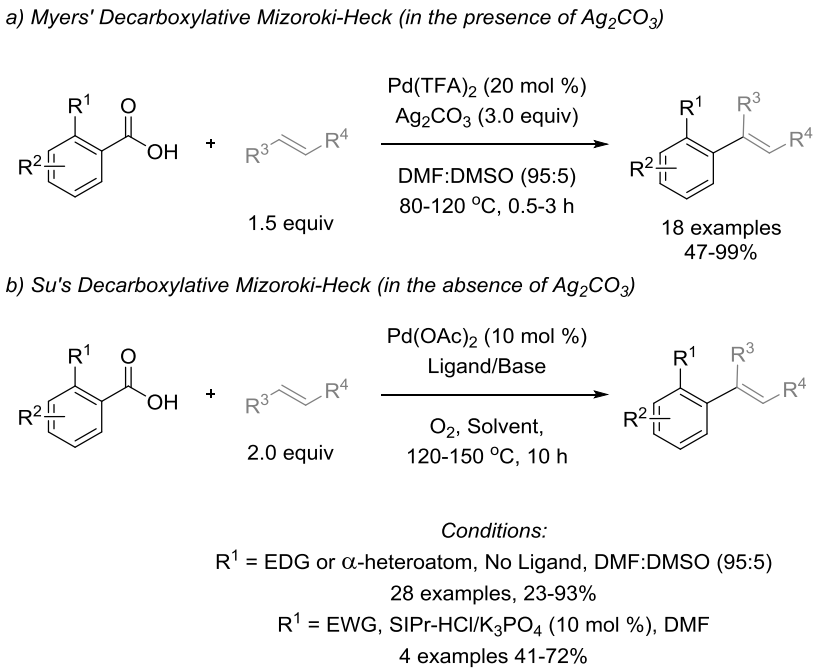
Using 2,6-dimethoxybenzoic acid as the model substrate, Kozlowski *et al.* generated the corresponding aryl-Pd species *in situ* using a stoichiometric amount of $Pd(TFA)_2$ and investigated the effect of different hydrogen sources on the reduction of this intermediate. Reaction with H_2 gas was sluggish giving only 43% conversion over 3 hours; a number of hydrosilanes ($HSi(Et)_3$, $HSi(i\text{-}Pr)_3$, $HSi(Ph)_3$) also proved successful with yields ranging from 59-82%. Several other hydrogen sources were tested including Mg/NH_4OAc in MeOH, which has been proposed to generate H radicals.[52] The most successful hydride source tested was polymethylhydrosiloxane (PMHS) in combination with KF which afforded 95% conversion in 30 min at room temperature. Unfortunately a protocol which involves the catalytic decarboxylation in the presence of hydride sources is not viable as all attempts by Kozlowski *et al.* to develop this methodology using 20 mol % $Pd(TFA)_2$ resulted in poor yields due to the formation of palladium black, which could not be prevented even with the addition of a oxidant.

During investigation into the effect of hydrogen sources on the protodemetallation step, Kozlowski *et al.* noted that the protodepalladation could occur in the absence of an additional proton/hydride source however the reaction is very slow. In this case the proton arises from the initial ligand exchange step which releases a stoichiometric amount of TFA (Scheme 34). The effect of acid concentration was probed using methanesulfonic acid ($MeSO_3H$) due to its decreased volatility; protonation occurred much slower when 1 equiv ($k = 5.3 \times 10^{-7}$ s^{-1}, $t_{½} = 365$ h) or 3 equiv of $MeSO_3H$ was added ($k = 3.3 \times 10^{-6}$ s^{-1}, $t_{½} = 58$ h) as opposed to the standard 10 equiv ($k = 1.3 \times 10^{-5}$ s^{-1}, $t_{½} = 14$ h). Determination of the free energy of activation for the decarboxylative palladation and protodepalladation steps using Eyring analysis concluded that the protonation step is the rate-determining step of the overall reaction (decarboxylation $\Delta G^{‡}_{298} = 25$ kcal mol^{-1}; protonolysis $\Delta G^{‡}_{298} = 27$ kcal mol^{-1}), at least for 2,6-dimethoxybenzoic acid.

It has been established that the addition of acid is required in the Pd-catalysed protodecarboxylation to facilitate catalytic turnover, thus permitting the use of sub-stoichiometric amounts of Pd salts. In the absence of acid, this turnover-limiting step is sluggish and the addition of hydride sources to promote formation of the C(aryl)−H bond result in off cycle reduction of the Pd catalyst and thus poor conversion. However, the addition of acid results in rate retardation of the decarboxylation step; in the presence of 10 equiv of $MeSO_3H$ the rate slows by 5 fold ($k = 1.7 \times 10^{-4}$ s^{-1}, $t_{½} = 1.2$ h) compared to when no acid is added ($k = 8.8 \times 10^{-4}$ s^{-1}, $t_{½} = 13$ min). Therefore, despite being necessary for protonolysis (and hence catalyst regeneration) the addition of acid plays an inhibitory role on the decarboxylation event.

1.4.4. – A comparison of Myers' and Su's Pd-catalysed decarboxylative Mizoroki-Heck conditions

In 2010, Su and co-workers[53] reported an alternative Pd-catalysed decarboxylative Heck reaction (Scheme 35b) compared to the initial reports by Myers *et al.*[36,37] (Scheme 35a). In this subsequent report, the reaction used O_2 as the terminal oxidant negating the requirement of Ag_2CO_3 and rendering the process mono-metallic. Similar to Myers' protocol, Su's methodology tolerates a wide variety of substituents, and although the reaction conditions do vary, it is worth noting that substrates containing electron-donating groups at the *ortho* position or heteroatoms in α can be reacted at 120 °C without the addition of a ligand. However, acids bearing electron-withdrawing groups in *ortho* require the addition of an NHC ligand (and base to form the NHC-Pd complex) and elevated temperatures (150 °C). This suggests that Pd-catalysed decarboxylation of electron-deficient acids is not facile and requires an electron-rich Pd centre and elevated temperatures to occur; this is in contrast to Myers' protocol where Ag is likely mediating decarboxylation for these substrates.

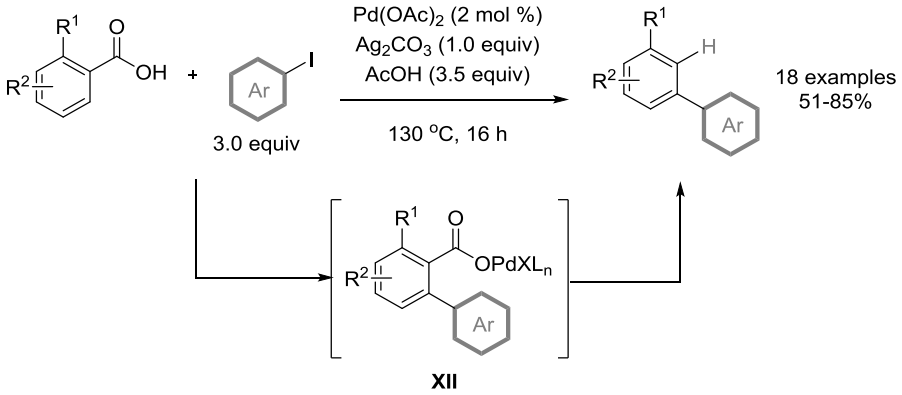


Scheme 35. Comparison of the conditions reported by a) Myers[36] and b) Su[53] for the decarboxylative Mizoroki-Heck-type vinylation reaction employing Ag_2CO_3 or O_2 as the oxidant, respectively.

With regards to the anomalous result of 2-nitrobenzoic acid in Liu's mechanistic study of Myers' Heck vinylation, the comparison of Su and Myers' conditions adds additional evidence to the conclusion that in Pd-catalysed decarboxylative transformations, where Ag salts are employed as a base and oxidant, it is likely that Ag may also play a supplementary role in facilitating the decarboxylation of electron-deficient substrates instead of Pd, as is often claimed (*vide supra*).

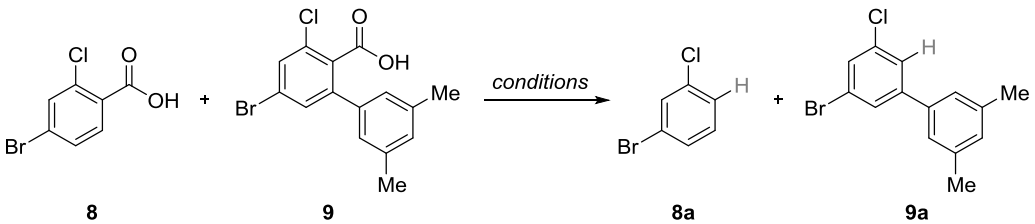
1.4.5. – Pd-catalysed decarboxylation of sterically hindered substrates

Recently Larrosa and co-workers reported the formal *meta*-arylation of benzoic acids with aryl iodides (Scheme 36).[54] The reaction proceeds via a directed C–H arylation *ortho* to the carboxyl moiety followed by decarboxylation of the arylated intermediate **XII**. For some products additional heating in Ag_2CO_3 and DMSO was required after the initial 16 h to achieve full protodecarboxylation. However, the majority of products underwent complete decarboxylation under the reaction conditions.



Scheme 36. Pd catalysed *meta*-arylation reported by Larrosa *et al.* The protocol uses the carboxyl moiety as a traceless directing group to control Pd-catalysed *ortho* arylation then removal via subsequent decarboxylation.[54a]

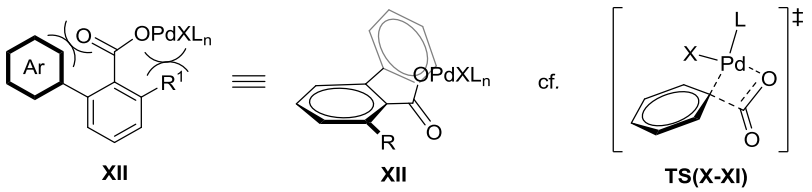
As mentioned previously, the decarboxylation of benzoic acids solely using Pd(II) salts, is limited to electron-rich substrates. However, the protocol described by Larrosa *et al.* tolerates the decarboxylation of compounds containing a variety of substituents, including electron-withdrawing fluoro and chloro substituents at the *ortho* position. Through competition experiments it was established that in this system Pd(II) can exclusively promote the decarboxylation of substrates which are atypical candidates for Pd-catalysed decarboxylation. Furthermore, they were able to show that the reaction conditions favour decarboxylation of the product over the starting benzoic acid (Scheme 37).



	8a	9a
Ag_2CO_3 (10 mol %), DMSO, 120 °C, 4 h	18%	5%
Ag_2CO_3 (1.0 equiv), AcOH, 130 °C, 2 h	0%	0%
$Pd(OAc)_2$ (2 mol %), AcOH, 130 °C, 2 h	0%	22%
$Pd(OAc)_2$ (2 mol %), Ag_2CO_3 (1.0 equiv), AcOH, 130 °C, 16 h	0%	5%

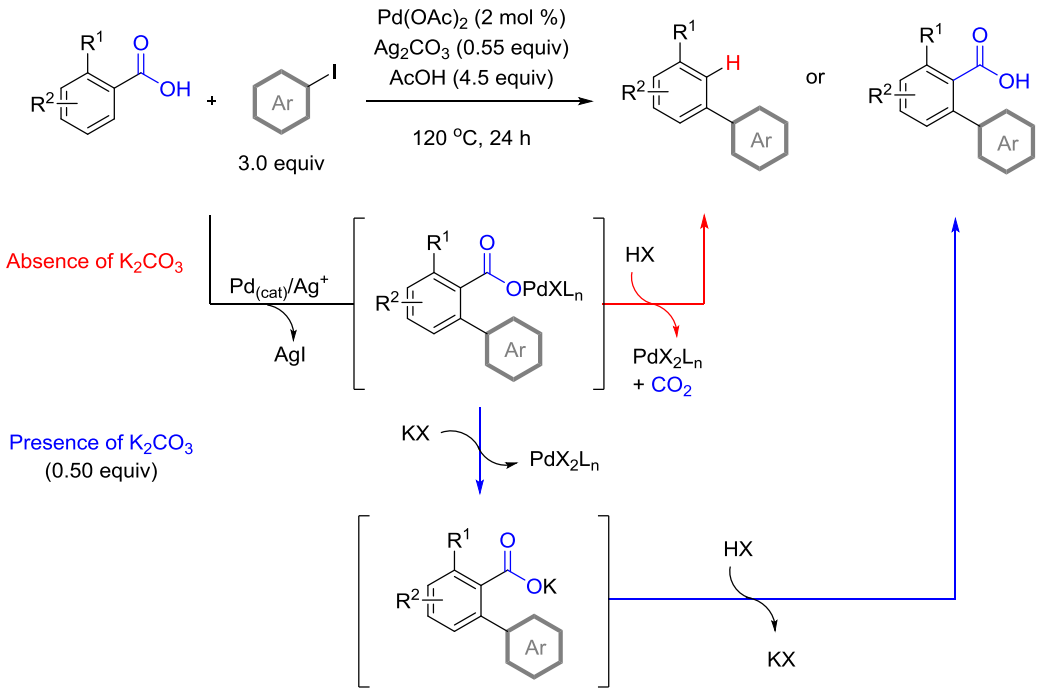
Scheme 37. The decarboxylation of **9** is catalysed by Pd whilst no decarboxylation of the starting material **8** is observed under the reaction conditions.[54a]

In their DFT study on the $Pd(TFA)_2$/DMSO mediated decarboxylation of benzoic acids, Lin and Su noted that the overall barrier to decarboxylation is lower for substituents which are highly electron-rich (e.g. methoxy substituted benzoic acids).[23] However, the barrier to decarboxylation is reduced for *ortho* isomers in comparison to their *meta* and *para* analogues, regardless of electronics, therefore steric hindrance plays an important role in reducing the overall barrier to decarboxylation by destabilising the *ortho* substrate (cf. *meta* and *para*). Accordingly, in the $Pd(OAc)_2$/AcOH system reported by Larrosa *et al.* it is likely that the increased steric effect of the *ortho* aryl group following arylation helps to lower the barrier to decarboxylation by offering a further destabilisation of the bis-*ortho*-substituted product in comparison to the *ortho* substituted starting material. As shown in Scheme 38, this additional aryl group may prevent co-planarity of the carboxylate group forcing the starting material into a conformation approaching that of the transition state structure observed by Lin and Su (Scheme 34, **TS(X-XI)**), where the carboxylate and Pd-centre are perpendicular to the ring.

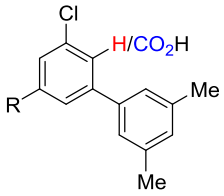


Scheme 38. Due to the planarity requirement of the biaryl to maximise overlap of the π-system, the additional aryl group may force the carboxylate into geometry close to that of the decarboxylation transition state.

The unprecedented steric control of the Pd-catalysed decarboxylation has been further exploited by Larrosa and co-workers towards the *meta*-arylation of phenols whereby a carboxylic acid was utilised as a traceless directing group; via carboxylation, carboxylate directed arylation and subsequent *in situ* decarboxylation.[55] Furthermore, by modifying the conditions of the initial *meta*-arylation protocol, shown in Scheme 36, the Pd-catalysed decarboxylation could be overridden to favour formation of the arylated benzoic acids (Scheme 39).[56] In the absence of K_2CO_3 the Pd-carboxylate is formed after arylation and can undergo decarboxylation; however on the addition of the potassium base the K-carboxylate is formed which is unable to decarboxylate and protonates to form the arylated benzoic acid. The ability of metal salts to hinder decarboxylation was also observed in the control experiments shown in Scheme 37, whereby the addition of 1 equiv of Ag_2CO_3 reduced the amount of protodecarboxylated biaryl observed, even after prolonged reaction times (with 1 equiv Ag_2CO_3 over 16 h ⟶ 5% product; cf. no Ag_2CO_3 over 2 h ⟶ 22 % product).



Examples:



R	With K_2CO_3		Without K_2CO_3	
	Yield	H:CO_2H	Yield	H:CO_2H
F	70%	**5:95**	87%	**9:91**
Cl	79%	**6:94**	94%	29:71
H	82%	**3:97**	76%	49:51

Scheme 39. Overriding the Pd-catalysed decarboxylation for the direct-*ortho*-arylation of benzoic acids.[56]

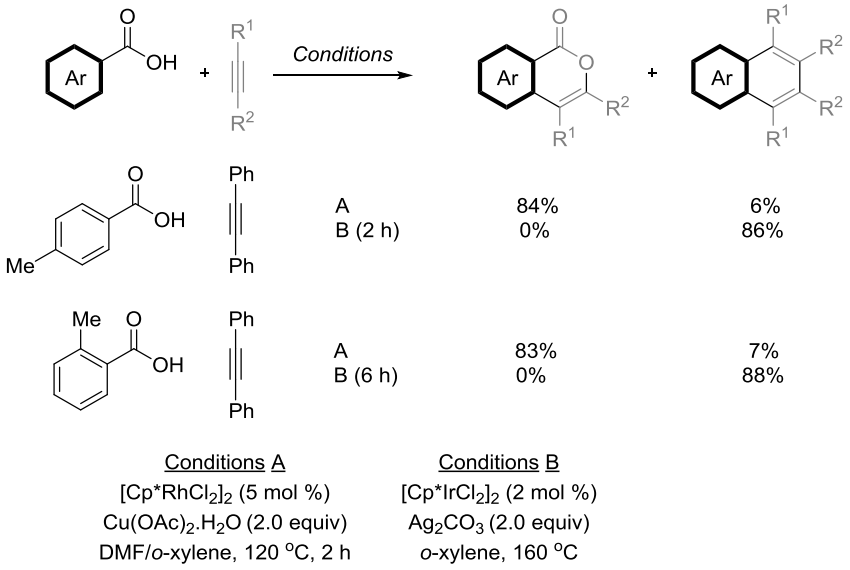
1.5. – RHODIUM-MEDIATED DECARBOXYLATIVE ACTIVATION

1.5.1. – Discovery

The decarboxylation of Rh-carboxylates was first reported in the late 1970's during the attempted oxidation of Rh(I)-carboxylates with thallic acetate or trifluoracetate,[57] and on decomposition of Rh(I)-carboxylates obtained through C–H carboxylation.[58] In 1980, Deacon and co-workers observed the formation of perfluoroaryl-rhodium complexes via decarboxylation of the corresponding Rh(I)-carboxylates in pyridine. Accompanying studies on the reaction rates were reported with electron-deficient substrates being more reactive (Ar = C_6F_5 > *p*-$MeOC_6F_4$ > *p*-HC_6F_4 > *m*-HC_6F_4 > 4,5-$H_2C_6F_3$ > 3,5-$H_2C_6F_4$).[59]

1.5.2. – Applications of the Rh-catalysed decarboxylation

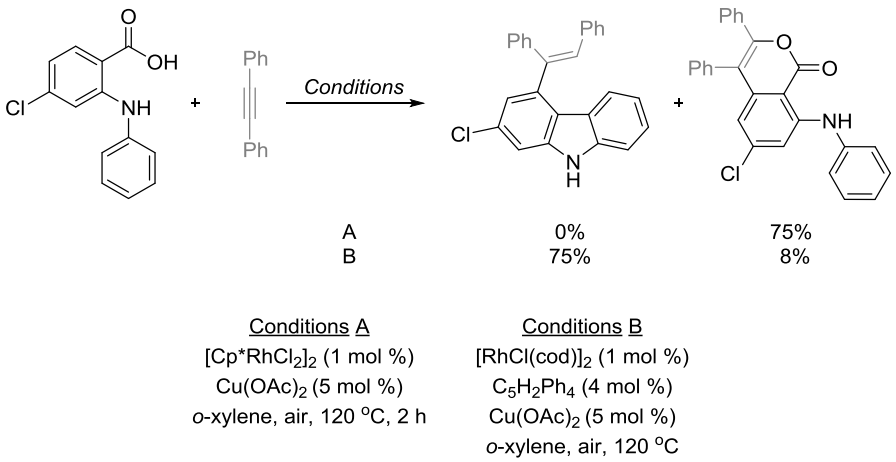
Despite the early studies on the formation and decomposition of Rh(I)-carboxylates, it was around 30 years until a methodology was reported that utilised this decarboxylative activation of rhodium. In 2007, Miura and Satoh reported an oxidative coupling of benzoic acids and alkynes towards the synthesis of isocoumarin and naphthalene derivatives (Scheme 40).[60] When [Cp*$RhCl_2$] was employed as the catalyst in conjunction with super-stoichiometric amounts of Cu(II) as the oxidant, the isocoumarin derivatives were observed as the major product with small amounts of naphthalene arising due to Rh-catalysed decarboxylation.



Scheme 40. Oxidative coupling of benzoic acids and alkynes reported by Miura and Satoh. Different product distributions can be achieved by changing the metal.[60]

Cu salts are used in the transformation shown in Scheme 39, and are well known to facilitate the decarboxylation of benzoic acids. However, due to the solvent utilised in the transformation (DMF or *o*-xylene), the absence of an additional ligand and the nature of the substituents on the benzoic acid suggests that it is unlikely Cu is facilitating the decarboxylation. Furthermore, when the catalyst system was changed to [Cp*$IrCl_2$], with Ag_2CO_3 being the preferred oxidant, the reaction favours formation of the naphthalene derivatives via an alkyne insertion-decarboxylation-alkyne insertion mechanism to construct the fused benzene ring. Similar to the argument discussed above for the Rh/Cu mediated transformation it is likely that indeed Ir is catalysing the decarboxylation in this case and not Ag.

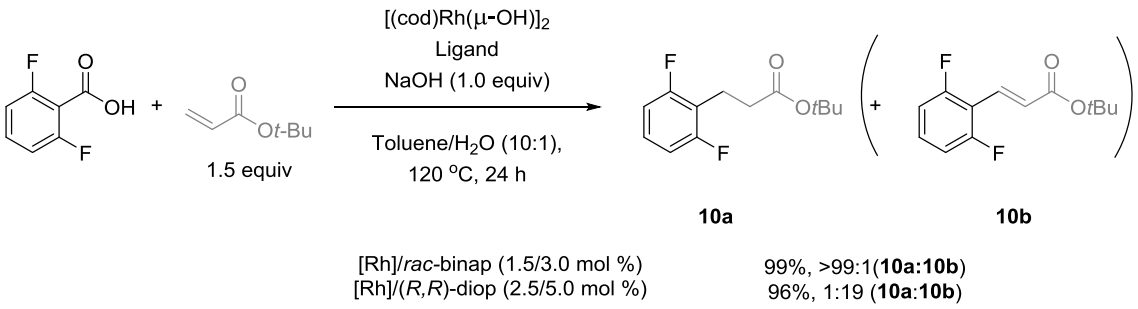
Subsequently, Miura and Satoh reported the application of the Rh/Cu system for the formation of vinylated carbazoles through the oxidative coupling and decarboxylation of *N*-phenylanthranillic acids and alkynes (Scheme 41).[61] Similar to the previous methodology outlined in Scheme 40, formation of isocoumarin derivatives occurs via a competing pathway; however in this case either pathway can be favoured by changing the ligand on Rh and the solvent.



Scheme 41. Oxidative coupling of anthranillic acids and alkynes reported by Miura and Satoh. By changing the Rh catalyst and solvent the reaction can be tuned to favour formation of the vinylated carbazole or isocoumarin.[61]

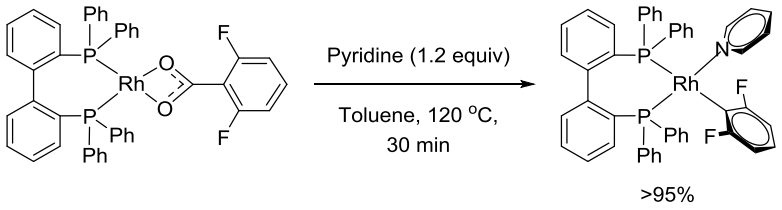
To date, the only other examples of Rh catalysed decarboxylation in the literature have been reported by Zhao and co-workers.[i] In 2009, Zhao *et al.* reported the decarboxylative conjugate addition of fluorinated benzoic acids (Scheme 42).[63]

[i] Other Rh catalysed methodologies have been employed for the cross-coupling of benzoic acid derivatives however they proceed via a decarbonylation pathway commonly involving Rh insertion into a pivaloyl ester, anhydride or acyl chloride followed by decarbonylation then reductive elimination.[1b,62]



Scheme 42. Rh-catalysed decarboxylative conjugate addition of fluorinated benzoic acids reported by Zhao *et al.*[63]

The reaction proceeds via generation of an aryl-Rh species through decarboxylation. The structure of this was confirmed through stoichiometric studies and X-Ray crystallographic characterisation (Scheme 43). Subsequently, the aryl-Rh complex then undergoes conjugate addition to the alkene forming an alkyl-Rh intermediate which can protodemetallate to generate the major aliphatic product **10a** or undergo β-hydride elimination to form the minor Mizoroki-Heck type product **10b**.



Scheme 43. Zhao and co-workers showed through stoichiometric studies that Rh(I)-carboxylates can extrude CO_2 to form the corresponding aryl-Rh(I) species in 30 mins, the structures were confirmed by X-Ray crystallography.[63]

Zhao's conjugate addition protocol employs H_2O as the co-solvent which likely hydrolyses the metallated conjugate addition product; however, this mechanism also occurs in dry toluene (albeit with worse regioselectivity) and seems to be a highly favourable pathway. Zhao and co-workers found that the regioselectivity could be switched by changing the ligand system (from *rac*-binap to (*R,R*)-diop).[63,64] A subsequent mechanistic paper by Shi determined through DFT calculations that the change in regioselectivity was attributed to a switch between diffusion and kinetic control when the water content of the solvent mixture was increased.[65] Furthermore, ligand control appears to adjust the interaction between the Rh-enolate intermediate and H_2O resulting in a destabilisation of the intermediate with respect to the hydrolysis pathway in addition to a reduction in the β-hydride elimination pathway.

The Rh-catalysed protodemetallation of benzoic acids was also reported by Zhao and co-workers in their 2010 paper.[64] The main types of substituents reported in the decarboxylation methodologies

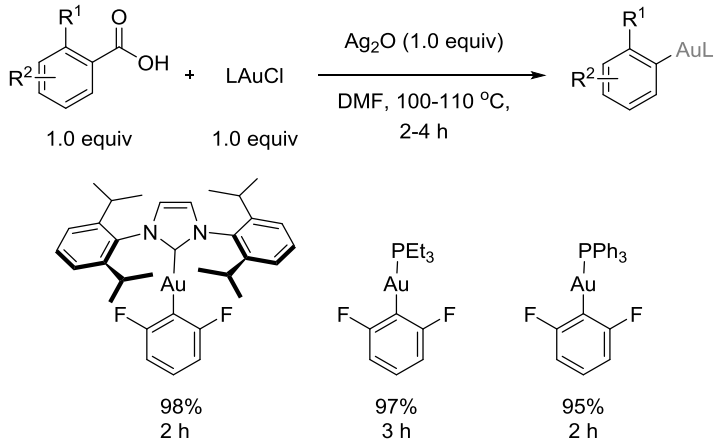
are those that have F, NO_2 and OMe groups and one examples of a heteroarene (3-indole-carboxylic acid) which is a surprising example as most reports of decarboxylative activation of heteroarenes are on substrates with a heteroatom α to the carboxyl moiety (*vide infra*). Similar to the case of the Pd-catalysed methodology, two substituents in *ortho* are required for good yields. Using Rh catalysis 2-fluorobenzoic acid only reacts in 8% over 24 h at 150 ^{o}C whereas 2,6-difluorobenzoic acid reaches 93% conversion in 8 h at a lower temperature (110 ^{o}C). The lack of reactivity of the mono-substituted substrates may be due to a competing *ortho*-insertion pathway.

In the computational study of Zhao's Rh-catalysed decarboxylative conjugate addition, Shi focuses on the factors controlling regioselectivity between the hydrolysed and Mizoroki-Heck products (**10a** and **10b**, respectively). The decarboxylation mechanism to generate the aryl-Rh(I) intermediate is calculated to be exergonic with an activation barrier of 28.7 kcal mol^{-1}, which is less than the values calculated for the Ag- and Cu-catalysed processes (34.0-35.0 kcal mol^{-1}) however these values are calculated from benzoic acid and not the di-fluorinated benzoic acid which is likely to have a reduced barrier to activation. The effect of substituents is not thoroughly investigated in any of the manuscripts. However, knowledge on the breadth of the substrate scope would be highly useful, as the Rh protocol employs very low loadings of catalyst (1-3 mol %) in solvent systems (toluene or H_2O/toluene) which offer easier purification than the high boiling, polar solvents usually required in decarboxylative transformations. Furthermore, the requirement of a ligand on Rh allows for the fine-tuning of the steric and electronic properties of the metal centre which can open new avenues to a variety of applications in synthesis.

1.6. – GOLD-MEDIATED DECARBOXYLATIVE ACTIVATION

1.6.1. – Discovery

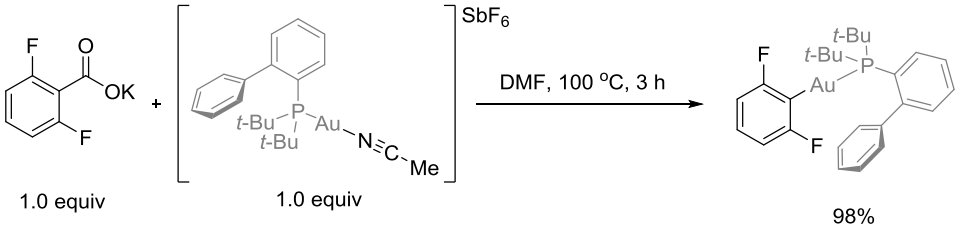
In 1991, Fackler Jr. *et al.* demonstrated that when lactate and benzoate (triphenylphosphine)gold(I) carboxylates were heated to reflux in aromatic solvents, decarboxylation could occur via a radical pathway involving homolysis of the Au(I)–O bond.[66] This led to subsequent formation of free triphenylphosphine, deposition of metallic Au and a distribution of products formed from the respective alkyl or aryl radicals.



Scheme 44. The formation of aryl-Au species via decarboxylative activation was reported by Larrosa *et al.* in 2011.[67]

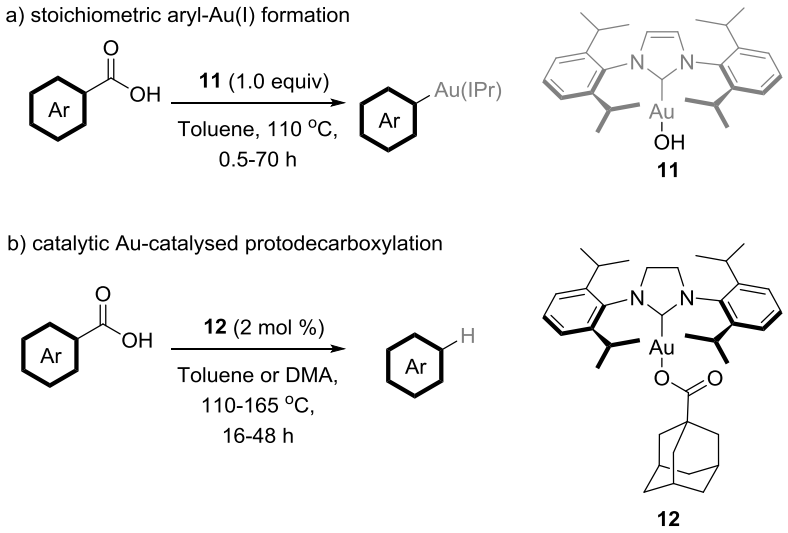
In 2011 Larrosa and co-workers showed that *ortho*-substituted benzoic or α-heteroaromatic acids could be utilised to access aurated compounds through a novel decarboxylation pathway (Scheme 44).[67] Unlike the reports by Fackler Jr *et al.* no radical coupling products were observed, instead high yielding formation of stable aryl-Au(I) compounds was achieved. The stability of these aryl-gold compounds is remarkable considering that they can be purified by standard chromatographic techniques and other group 11 metallated species are notoriously unstable and readily undergo protonolysis when generated *in situ*.

The protocol shown in Scheme 45 employs stoichiometric amounts of silver salts, however their role is solely to act as a halide abstractor and base to generate the Au(I)-carboxylate *in situ*. The ability of Au to mediate the decarboxylation was exclusively shown by utilising the potassium salt of 2,6-difluorobenzoic acid and cationic Au(I)-source (Scheme 44), in this manner the decarboxylation could be carried out under silver-free conditions.



Scheme 45. The decarboxylation of benzoic acids can unequivocally occur in the absence of Ag with pre-formation of the carboxylate and using a cationic source of Au.[67]

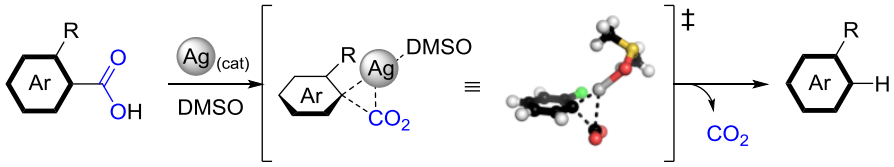
Using a NHC ligated IPrAu(I) hydroxide catalyst, Nolan *et al.* have also shown that a variety of aryl-Au(I) species can be accessed via a decarboxylative pathway.[68] Furthermore, they have demonstrated that similar to the Pd-catalysed protodecarboxylation reaction, in the presence of acid, the Au-catalysed protodecarboxylation can occur either using the more electron-rich SIPrAu(I)-hydroxide catalyst and a stoichiometric amount of adamantoic acid or from the preformed SIPrAu(I) adamantoate with low catalyst loadings (2 mol %) (Scheme 46).[68b]



Scheme 46. Nolan *et al.* also reported the formation of aryl-Au complexes [a)][68a] in addition to a Au-catalysed protodecarboxylation methodology [b)][68b].

The Au-catalysed decarboxylation methodologies presented to date exhibit the widest substrate scopes of all the aromatic decarboxylation methodologies reported herein; with electron-donating groups, heteroaromatic acids and most strikingly the reports of non-ortho-substituted acids decarboxylating in good yields at 140 °C, however this is limited to electron-rich groups in the para position and the use of deactivating groups such NO_2 or bromo in the *meta* position require more forcing temperatures (165 °C). Until recently, the favoured solvents for decarboxylations were polar high-boiling compounds such as DMF, DMA, DMSO, NMP and quinolone, however recent reports on the Au, Pd and Rh catalysed protodecarboxylation systems have shown that in some cases decarboxylations can be facilitated in apolar solvents such as toluene and xylenes and in aqueous mixtures.

1.7. – AIM OF THE PROJECT



In the last few years it has been demonstrated that Ag catalysts are very efficient at promoting decarboxylation at lower temperatures. Interestingly, this reaction can only be facilitated in the presence of an *ortho*-substituent. Initial observations suggest that this substituent can be either electron-withdrawing or strongly electron-donating and that the regiospecificity of the reaction is directly related to the effect that the *ortho* substituent imparts. Further understanding of the nature of this *ortho*-effect would be of immense value, allowing for the design of novel catalysts and the prediction of reactivities of unknown substrates.

To date, only one study has been published on Ag/DMSO system.[22] In which the authors determine that most isomers of substituted benzoic acids have degenerate transition states; however, *ortho* isomers have lower activation energies. The *ortho* group causes an inherent destabilisation of the starting material resulting in an overall reduction of the barrier to decarboxylation. Naturally, this effect cannot occur in *meta* and *para* substituted benzoic acids and thus rationalises their lack of reactivity in this system.[25a]

The main conclusion drawn by the authors was that the *ortho* effect is purely steric in nature and no correlation was found with the substituent's electronic properties. This seems contrary to our experience, so we have carried out a broader mechanistic study involving both theoretical and experimental analysis to gain a greater understanding. Consequently, the free energies of activation for a variety of benzoic acids with substituents of varying polarities and sizes were calculated using DFT. The initial rates of reaction were determined for this set, allowing for direct comparison of theoretical and experimental results using the Eyring equation.

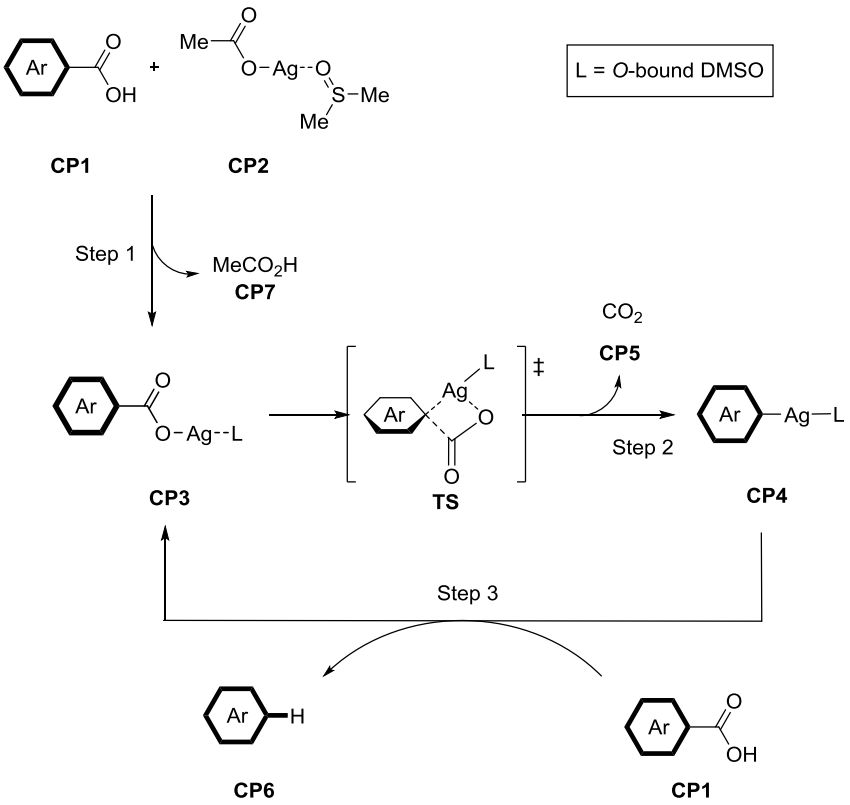
A study that results in an improved understanding of the factors that affect decarboxylation would be highly beneficial to researchers in this field. Furthermore, if a quantifiable system of relative rates of decarboxylation for a given substrate can be generated, based upon theoretical calculations, polarity constants and/or steric bulk, it may be possible to predict the reactivity of untested substrates or allow for catalyst design to improve reactivity in the future.

[ii] All of the computational modelling (DFT) discussed in this Chapter was carried out by Dr. J. M. Campanera, Lecturer in Physical Chemistry at the University of Barcelona.

1.7. – INVESTIGATING THE *ORTHO* EFFECT

1.7.1. – Mechanism of the Ag-catalysed decarboxylation of benzoic acids

Previous work in the group has focused on the development of a Ag(I)-catalysed decarboxylation of aromatic carboxylic acids using DMSO as the solvent.[25] The proposed catalytic cycle for such a transformation is depicted in Scheme 47, and is in line with that proposed by Lin and Su in their 2011 study.[22] The cycle is composed of three steps: step 1) the initial ligand exchange via an acid-base reaction leading to the catalytically active species **CP3**; step 2) the decarboxylation, which is rate-determining and therefore contains the most energetically demanding transition state (**TS**), and finally step 3) regeneration of the catalyst via protodemetallation of aryl-Ag species **CP4** and formation of the product (**CP6**).



Scheme 47. Proposed mechanism for the Ag(I)-catalysed decarboxylation of (hetero)aromatic acids.

The activation energy accounts for the free energy of formation of the transition state (**TS**) from the Ag-benzoate (**CP3**) (Scheme 47, Step 2). For the Ag(I)-catalysed decarboxylation of *ortho*-chlorobenzoic acid, the activation barrier value is calculated to be 25.3 kcal mol^{-1}, which is in line with the values calculated by Lin and Su ($\Delta G^{\ddagger}_{(Ag)}$ = 28.1 kcal mol^{-1}, $\Delta G^{\ddagger}_{(Cu)}$ = 26.6 kcal mol^{-1}).[22] In thermodynamic terms, the overall decarboxylation process for *ortho*-chloro benzoic acid is exergonic

(ΔG^{rel} = −19.5 kcal mol^{-1}) in which both the initial ligand exchange (step 1) and the decarboxylation (step 2) involve a low energy requirement (−1.7 and −2.1 kcal mol^{-1}, respectively) and the catalyst regeneration is extremely exergonic (−15.7 kcal mol^{-1}).

1.7.2. – A specific comparison of *ortho*-, *meta*- and *para*-chloro benzoic acid

In order to study the effect of substitution in the ring, the three isomers of chlorobenzoic acid were initially studied. Experimental results have demonstrated that in this system, only *ortho*-chlorobenzoic acid decarboxylates while the *meta and para* isomers, and benzoic acid itself, remain unreactive (Table 1). This is supported by the present theoretical results for the four mentioned compounds: *ortho*-Cl reacts with a much lower activation energy, +25.3 kcal mol^{-1} when compared to the other substrates (+27.0, +28.1 and +28.4 kcal mol^{-1}, respectively) (see Table 1).

Table 1. Comparison of the theoretical and experimental reactivities for Cl-C_6H_4-CO_2H.[a]

Entry	R	$\Delta G^{‡}_{X}$ (kcal mol^{-1})[b]	$\Delta G^{‡}_{X} - \Delta G^{‡}_{H}$ (kcal mol^{-1})[b]	Conversion (%)
1	*ortho*-Cl	25.3	−3.0	37
2	*meta*-Cl	27.0	−1.4	0
3	*para*-Cl	28.1	−0.3	0
4	H	28.4	0	0

[a]Reaction conditions: all reactions were carried out under air atmosphere, 0.3 mmol of the benzoic acid and 20 mol % Ag_2CO_3 were heated to 120 ^{o}C in DMSO (0.2 M) for 16 h, conversion calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]$\Delta G^{‡}$ calculated using DFT with Becke-Perdew functional and TZP basis set (BP/TZP).

A graphical representation of the reactivity difference between *ortho*- and *para*-chlorobenzoic acids is outlined in Figure 2. The calculations indicate that to reduce the activation barrier to decarboxylation, either the **CP3** structure has to be destabilised or the TS structure has to be stabilised. The *ortho* isomer is the least stable of the **CP3** structures with a difference of +3.0 kcal mol^{-1} (cf. the *para* isomer); however, the corresponding transition state structures for both compounds are essentially degenerate (+0.2 kcal mol^{-1}). Therefore, since the *ortho* isomer starts from a more unstable structure but reaches a similarly energetic configuration in the transition state, this overall decrease in activation energy ($\Delta G^{‡}_{ortho}$ = +25.3 kcal mol^{-1} cf. $\Delta G^{‡}_{para}$ = +28.1 kcal mol^{-1}) implies an increased rate of decarboxylation for this chlorobenzoic acid compared to the other isomer.

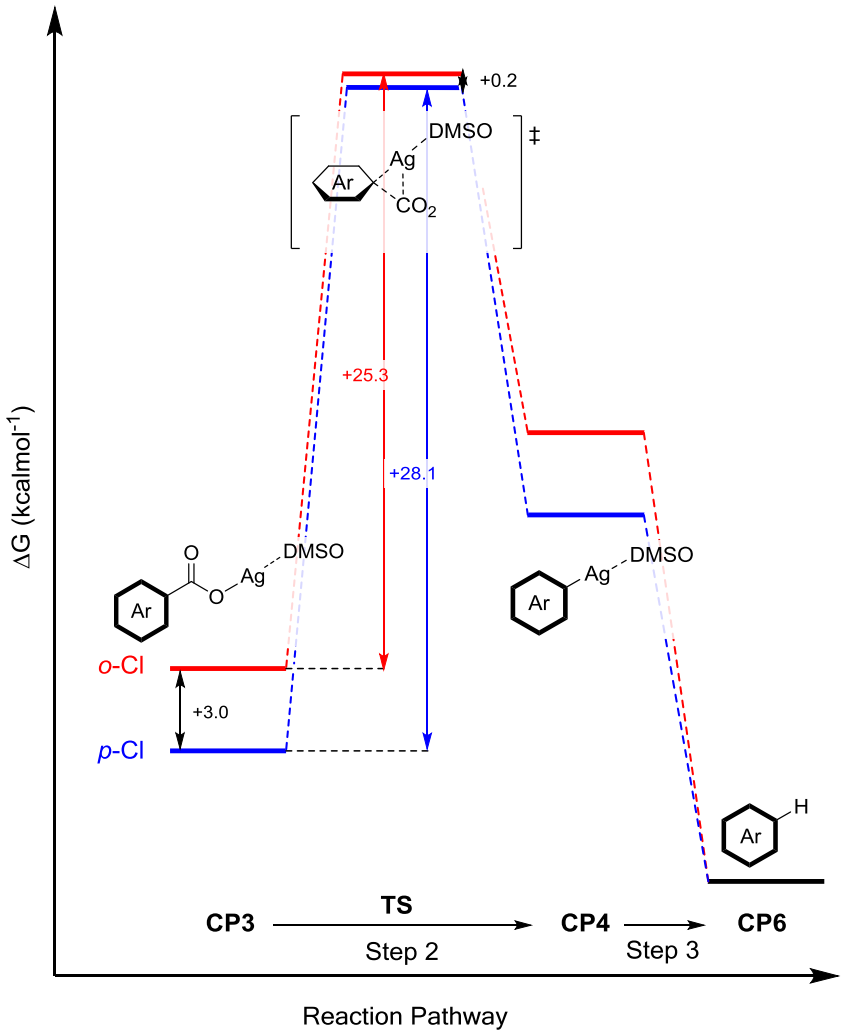
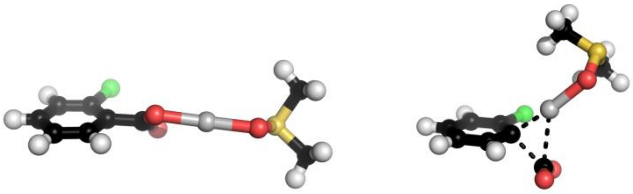


Figure 2. Archetypical energy profile for the decarboxylation of *ortho*- and *para*-chlorobenzoic acids. The reactivity of *ortho*-chlorobenzoic acid is exemplified by the destabilisation of the **CP3** substrate, leading to an overall reduction in the energy barrier to decarboxylation, relative to the *para* compound

.

The structural cause of the difference in **CP3**/**TS** stability among these isomers can be hypothesised in terms of the repulsive interaction between the *ortho* substituent and the carboxylic acid group in the **CP3** structure. Inherently, this proximity effect is significantly diminished in the **TS** structure and non-existent in the *meta* and *para* **CP3** substrates. This is illustrated by the increase in the average distance between the Cl atom and CO_2 moiety from the *ortho*-Cl **CP3** (3.52 Å) to the *ortho*-Cl **TS** (3.80 Å) as a consequence of steric relief (Figure 3). Similar steric effects that distinguish the reactivity of *ortho-, meta-* and *para*-isomers have been previously observed for Ag, Cu and Pd mediated decarboxylation reactions (*vide supra*).



ortho-Cl **CP3** *ortho*-Cl **TS**

Figure 3. Geometries of the reactant (**CP3**) and the transition state (**TS**) of the decarboxylation step for *ortho*-chlorobenzoic acid.

The observed reactivity differentiation among the three chlorobenzoic acids regioisomers prompted a deeper investigation into the factors that control the decarboxylation in this system. The activation energies for fourteen different acids bearing electron-withdrawing and donating substituents were computed with BP/TZP for each regioisomer (Table 2 (*ortho*–*para*), Table S1-2 (*ortho*–*meta*)). In every case, a notable decrease in the activation barrier was observed for the *ortho* isomer (cf. *para*) except for acids containing Me, CN, NH_2 and OH substituents. Table 2 shows the relative stability of the **CP3** and **TS** energies for different substrates which allows examination of the substituent effects on the **CP3** and **TS** in terms of their steric and electronic contributions.

Table 2. Comparison of the relative stability of **CP3** and **TS** structures for ortho and para isomers of several substituted benzoic acids versus the relative BP activation barriers for decarboxylation.[a]

Entry	R[a]	**CP3** G_{ortho}–G_{para} (kcal mol^{-1})	**TS** $G^{\ddagger}_{ortho} - G^{\ddagger}_{para}$ (kcal mol^{-1})	$\Delta G^{\ddagger}_{ortho} - \Delta G^{\ddagger}_{para}$ (kcal mol^{-1})[j]	$\Delta G^{\ddagger}_{ortho}$	Reactive Isomer
1	CF_3	6.9	1.6	−5.3	25.3	*Ortho*
2	NO_2	4.3	−0.8	−5.1	23.1	*Ortho*
3	CHO	4.3	−0.4	−4.7	23.7	*Ortho*
4	O^{i}Pr	8.1	4.2	−3.9	24.6	*Ortho*
5	Br	3.1	−0.2	−3.3	24.1	*Ortho*
6	Et	3.3	2.1	−1.2	25.2	None
7	Cl	3.0	0.2	−2.8	25.3	*Ortho*
8	Me	3.3	3.6	0.3	25.5	None
9	OEt	4.9	1.3	−3.6	25.0	*Ortho*
10	CN	0.1	0.5	0.4	27.4	None
11	OMe	3.6	3.0	−0.6	26.4	*Ortho*
12	NH_2	−0.9	0.7	1.6	26.5	None
13	OH	−7.2	−3.4	3.9	31.2	None
14	F	2.4	−0.1	−2.5	24.4	*Ortho*

[a]Parameters calculated using DFT with BP functional and TZP basis set. [b]Substituents are ranked in order of decreasing substituent size (using Charton's upsilon parameters[69]).

1.7.3. – Investigating the *ortho* effect on the **CP3**

Similar to the case of the chlorobenzoic acids, the increased reactivity of many of the *ortho* isomers results from the difference in relative stability of the **CP3** structures with respect to their *meta* and *para* isomers. For instance, the **CP3** structure of *ortho*-nitrobenzoic acid is 4.3 kcal mol^{-1} destabilised in relation to the *para* isomer, but the transition state is only marginally stabilised by 0.8 kcal mol^{-1}, resulting in an overall reduction in the activation energy by 5.1 kcal mol^{-1} (Table 2, entry 2). This energy difference is enough to make the decarboxylation feasible for the *ortho* compound ($\Delta G^{‡}$ = +23.1 kcal mol^{-1}) while the *para* compound remains completely unreactive ($\Delta G^{‡}$ = +28.2 kcal mol^{-1}).

In the case of *ortho*-NO_2 benzoic acid, the substituent is one of the most sterically bulky groups and its sheer size impedes the co-planarity of NO_2 and COOH groups. Naturally, this steric hindrance is not present in the *meta* and *para* isomers (Figure 3). However, for the whole dataset only a rough correlation with the size of the substituent and the destabilisation of the **CP3** is observed, indicating that electronic effects might play an important role. For example, while substituent size varies in the order NO_2>Me>OMe, the **CP3** stabilisation energies change in the order NO_2>OMe>Me.

It is worth mentioning that, in the case of OH and NH_2 substituted acids, the barrier to decarboxylation for the *para* isomer is now more energetically favoured than the *ortho i*somer. This is due to the formation of hydrogen bonds between the substituent and the carboxylate unit, stabilising both the **CP3** and **TS** structures thus resulting in an overall increase in the barrier to decarboxylation.[22]

1.7.4. – Investigating the *ortho* effect on the **TS**

In order to analyse the electronic contribution of the *ortho* effect on the **TS**, the similarly sized *ortho*-Br and *ortho*-Me (van der Waals radii of 1.85 Å and 1.97 Å (average), respectively)[70] were compared. The effect of the steric clash in **CP3** leads to similar stabilisations (3.1 and 3.3 kcal mol^{-1}, Table 2, entries 8 and 5, respectively). However, both acids present remarkably different reactivities: after 16 h reaction under the standard conditions, *ortho*-toluic acid fails to decarboxylate whilst *ortho*-bromobenzoic acid reaches 50% conversion. This disparity is attributed to their significantly different electronic properties, as noted in the **TS** energies: the electron-withdrawing *ortho*-Br substituent stabilises the **TS** by −0.2 kcal mol^{-1}, whereas the weakly electron-donating *ortho*-Me substituent destabilises the **TS** by 3.6 kcal mol^{-1}, when compared to the energies of their *para* isomers. This combination of both steric and electronic effects yields an activation barrier of +24.0 kcal mol^{-1} for the *ortho*-Br and +25.5 kcal mol^{-1} for *ortho*-Me benzoic acids, respectively.

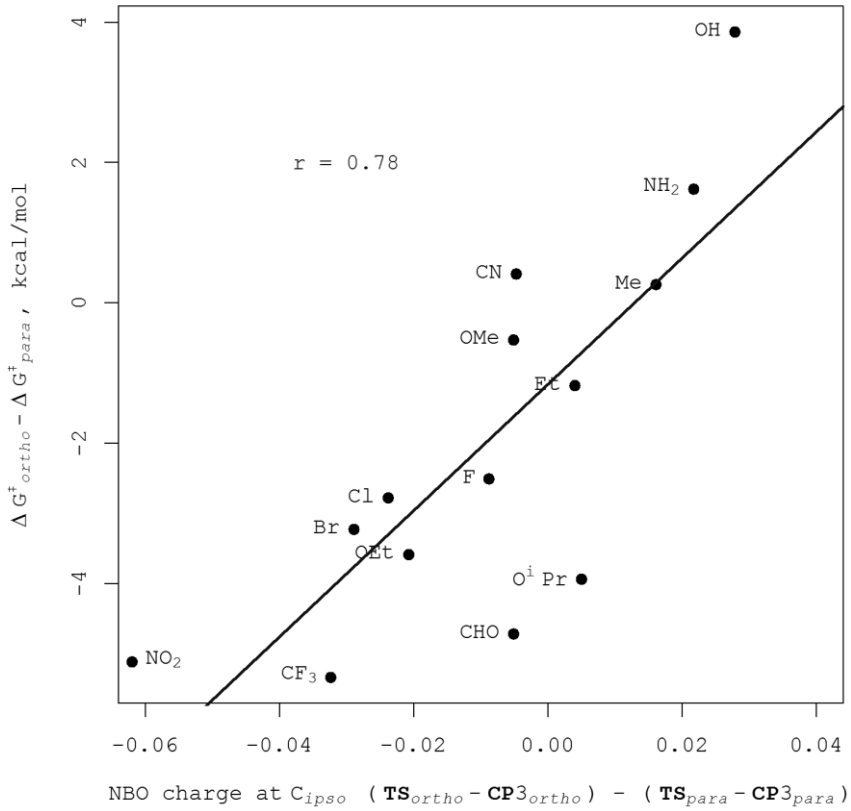


Figure 4. Correlation between $\Delta G^{\ddagger}_{ortho}$–$\Delta G^{\ddagger}_{para}$ and NBO double difference at C_{ipso} between **TS** and **CP3** structures and also between *ortho* and *para* compounds.

During the transition state, a build-up of electron density occurs at the *ipso* carbon during formation of the C(sp^2)–Ag bond and dissociation of the CO_2 fragment. The stabilising effect that the electron-withdrawing Br atom imparts is consistent with a reduction in the accumulating negative charge on the **TS** structure. In contrast, the inductively electron-donating Me group destabilises the transition state. To illustrate this concept, NBO (Natural Bond Orbitals)[71] charges at the *ipso* carbon of both isomers were calculated for the **TS** and **CP3** structures. Figure 4 shows that there is a significant correlation (r = 0.78) between the double difference NBO charges at the *ipso* carbon atom (*ortho*–*para* isomers) and the $\Delta G^{\ddagger}_{ortho}$–$\Delta G^{\ddagger}_{para}$ magnitude. This indicates that the electronic effect of the substituent has an overall effect on the activation energy and may not be limited to the stabilising influence on the **TS** structure. Comparable results are achieved using Mulliken charges (see Figure S1-2).

Interestingly, a destabilising steric effect on the **TS** is also observed for large substituents such as CF_3. Figure 4 shows that the relative NBO charge on the *ipso* carbon is similar in the case of *ortho*-CF_3

and *ortho*-F which adheres to the electron-withdrawing nature of the substituents. However, this similarity is not observed in the **TS** energy, where the *ortho*-CF_3 group actually destabilises the **TS** in relation to the *para* isomer (+1.6 kcal mol^{-1}), indicating that the beneficial steric effects on **CP3** may be outweighed in the **TS**.[iii]

1.7.5. – Experimental and theoretical agreement on the reactivity order

Once the influence of an *ortho* substituent in the Ag-catalysed decarboxylation of benzoic acids was determined to be a combination of steric and electronic factors, the next step was to explore the influence of different substituents, by comparing the activation energies calculated using the BP/TZP and M06/6-31G(d) methods and the experimental reaction rates for thirteen *ortho*-substituted benzoic acids (Table 3). In order to compare both experimental and theoretical values and validate the computational procedure, the Eyring equation was used to derive the experimental activation energies relative to *ortho*-CF_3 benzoic acid.

Table 3. Comparison of the theoretical and experimental activation energies for a variety of benzoic acids

Entry	R[a]	Initial Rate[b] (μmol min^{-1})	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{CF3}$ (exp.)[c] (kcal mol^{-1})	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{CF3}$ (theo. BP)[c,d] (kcal mol^{-1})	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{o\text{-}CF3}$ (theo. M06)[c,e] (kcal mol^{-1})
1	*o*-NO_2	−53.0	−3.1	−2.2	−3.3
2	*o*-F	−18.7	−2.3	−0.8	0.6
3	*o*-Br	−7.92	−1.6	−1.2	−0.3
4	*o*-Cl	−6.35	−1.4	0.1	−0.4
5	*o*-OMe	−4.27	−1.3	1.1	−0.7
6	*o*-OEt	−4.25	−1.1	−0.2	−1.5
7	*o*-O^{i}Pr	−4.01	−1.1	−0.7	−0.4
8	*o*-CF_3	−1.04	0.0	0.0	0.0
9	*o*-CN	unreactive	-	2.2	1.7
10	*o*-Me	unreactive	-	0.3	3.5
11	*o*-Et	unreactive	-	0.0	0.0
12	*o*-OH	unreactive	-	6.0	7.7
13	*o*-NH_2	unreactive	-	1.3	3.0
14	H	unreactive	-	3.1	4.5

[a]The compounds are ranked according to the energy of the experimentally calculated $\Delta G^{\ddagger}$ which was calculated using the Eyring equation. [b]Calculated using the initial rates method. [c]*ortho*-CF_3 used as a reference. [d]Energies calculated using BP/TZP. [e]Energies calculated using M06/6-31G(d).

[iii] The prominence of the *ortho* effect is also observed in the correlation between the $\Delta G^{\ddagger}_{ortho}$-$\Delta G^{\ddagger}_{para}$ difference and the activation energy barrier $\Delta G^{\ddagger}_{ortho}$, with a significant correlation coefficient (r) of 0.86 (Figure S1-3). Moreover, a correlation of 0.93 is observed when comparing the *ortho* and *meta* isomers (Figure S1-4). In line with this, there is also a positive correlation of 0.77 between C_{ipso}-CO_2 bond length difference in the **TS** and **CP3** structures and the activation energy for the *ortho* isomers (Figure S1-5). Therefore, compounds that require more structural changes between **CP3** and **TS** structures tend to be less reactive towards decarboxylation. This relationship imples that electron-withdrawing groups weaken the adjacent C_{ipso}-CO_2 bond by removing bonding electron density, indicating that the electronic influence is not limited to a stabilisation of the transition state structure.

Overall there is a moderate compliance between the experimental and theoretical relative activation energies (r = 0.77 for BP, Figure 5; r = 0.63 for M06, Figure S1-7, respectively). The general trend in Table 3 shows that inductively electron-withdrawing substituents (e.g. *ortho*-NO_2, *ortho*-F, *ortho*-Cl, *ortho*-Br) tend to be more activating than electron-donating substituents (e.g. *ortho*-Me, *ortho*-OH, *ortho*-NH_2).

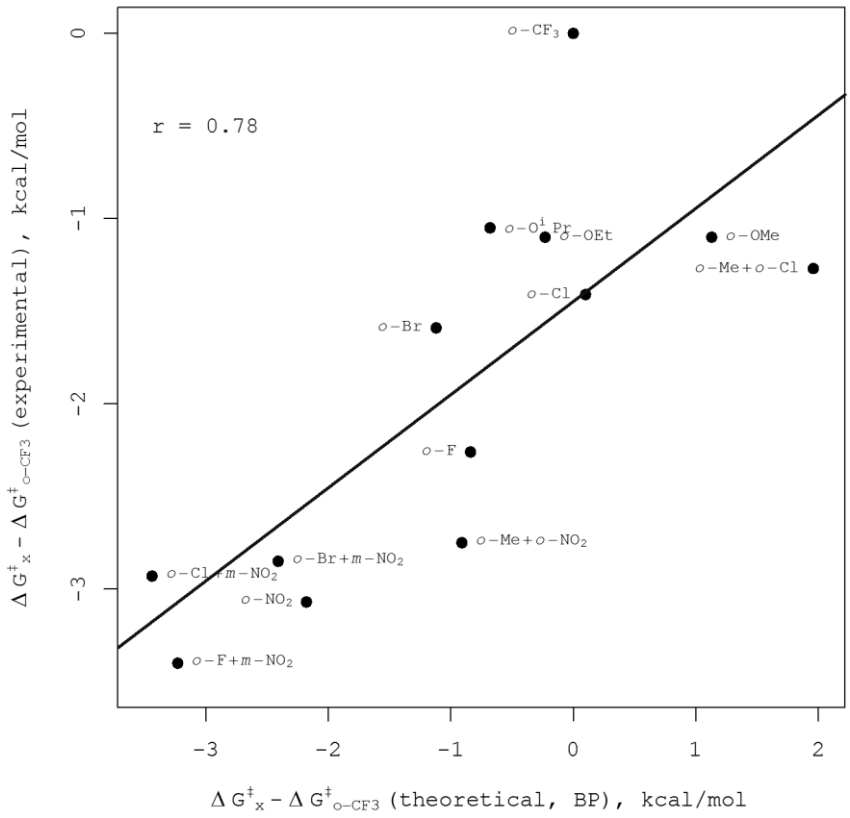


Figure 5. Statistically significant correlation between BP relative activation energy ($\Delta G^{\ddagger}_{BP}$) and experimental relative activation energy $\Delta G^{\ddagger}_{Experimental}$ for all thirteen tested compounds.

With these results in hand, the next goal is to establish a method to quantify the effect of electronic and steric parameters on the rate of decarboxylation; to achieve this a number of linear free energy relationships (LFERs) were investigated and the key aspects are discussed in the next section.

1.8. – LINEAR FREE ENERGY RELATIONSHIPS (LFERS) TO EVALUATE THE *ORTHO* EFFECT

1.8.1. – An overview of LFERs

Linear free energy relationships (LFERs) have played an important role in determining the influence that substituents impart on various reactions by correlating equilibrium and rate processes. One of the earliest examples is the Hammett equation (equation 1, Figure 6) which can be used to analyse the effect of a *meta* or *para* substituent on the rate of reaction.[72] The expression emerges from the correlation of the acidities of benzoic acids with the rates at which their ethyl ester hydrolyses. From these observations polar substituent constants (σ) have been defined for a variety of *meta* (σ_m) and *para* (σ_p) substituents which provide a measure of the total electronic influence (polar, inductive σ_I and resonance effects σ_R) in the absence of conjugation effects.[73] The reaction constant (ρ) provides a measure of reaction sensitivity to a substituent's electronic effects. With $\rho > 1$ indicating the reaction is more sensitive to substituent effects then benzoic acid − negative charge builds during the transition state and electron-withdrawing *g*roups can stabilise this; $\rho = 0$ indicates no substituent sensitivity; and $\rho < 1$ indicates the creation of positive charge during the reaction thus *electron donating* substituents are favoured.[74]

$$\log \frac{k_X}{k_{ref}} = \rho \sigma_{m,p} \quad (1)$$

k_x = rate of reaction of compound x;
k_{ref} = rate of reaction of reference compound, e.g. k_H = benzoic acid;
ρ = reaction constant; σ = substituent constant;
σ_m = effect of substituent in *meta* and inductive effect approximation (σ_I)
σ_p = effect in *para*
$\sigma_p - \sigma_m = \sigma_R$ = resonance effect (2)

Figure 6. The Hammett equation, a LFER that directly correlates the rate of a reaction to the polar constant of a substituent (σ), yielding a reaction constant (ρ).

Though well established, the Hammett relationship cannot be used to analyse the effect of an *ortho*-substituent as the σ values only account for the ordinary polar effect of a substituent and does not factor in any additional steric or polar proximity effects.[75] The first major attempt at a systematic treatment of *ortho*-substituted arenes by means of a LFER was carried out by Taft by separating the total *ortho*-substituent effect into polar (σ_o^*) and steric components E_S^o (Figure 7).[76]

$$\log\left(\frac{k_X}{k_H}\right)_A = E_S^o \quad (3)$$

$$\log\left(\frac{k_X}{k_H}\right)_B = \sigma_o^* + E_S^o \quad (4)$$

n.b. E_S = steric constant defined by Taft from the hydrolysis of aliphatic esters;

E_S^o = steric constant defined by Taft from the hydrolysis of *ortho*-substituted aromatic esters.[76b,77]

Figure 7. The Taft equation. This LFER was developed as an expansion of the Hammett equation, in order to account for the steric effects (E_S^o) of an *ortho*-substituent.

The Taft polar constant (σ_o^*) provides a similar function to the Hammett sigma constants (σ_m and σ_p) and has been calculated for aromatic, aliphatic and acyclic systems. The factor of 2.48 is included to make σ^* values comparable in scale to the Hammett constants. Taft also tried to quantify the steric effect of substituents by analysing the acid and base catalysed saponification of *ortho*-substituted benzoic esters (Figure 7, equations 3 and 4, respectively).

The Taft relationship and the E_S steric parameters have been shown to work well in the derivation of quantitative structure-activity relationships (QSAR) for variety of aliphatic compounds in living systems and for the optimisation of drug candidates.[78] However, the application of this model in aromatic systems has come under question with critics suggesting that Taft's steric parameters may include both electrical and steric effects.[79] Charton has attempted to resolve the uncertainty regarding the nature of E_S and E_S^o constants by carrying out correlations with modified variants of the extended Hammett equations (Figure 8, equations 7, 8).[80] Concluding that the E_S values are a function only of the space filling parameter of a substituent (as defined by the van der Waals radii); whereas the E_S^o steric constants are independent of the van der Waals radii and (with the exception of the phenyl group) can be completely accounted for in terms of electrical effect parameters. This led to the development of Charton's free energy relationship (Figure 8, equation 9) which has been used in a number of studies to evaluate the reactivity of a variety of substrates by correlating electrical (inductive and resonance) and steric properties of an *ortho* substituent using the van der Waals radii referenced to hydrogen. [81,80,82] However, Charton's relationship can only be used to investigate the electrical and steric parameters of a contiguous set of mono-*ortho*-substituted arenes, and cannot be used to evaluate a variety of mono-, di- or poly-substituted arenes simultaneously.

$$Q_X = \sigma_{I,X} + \sigma_{R,X} + h \quad (5)$$

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi\zeta_X + h \quad (6)$$

$Q_X =$ total electrical effect of substitutent x
n.b. $\zeta_X \equiv r_{v,X} \equiv \sigma_{v,X}$ = van der Waals radii relative to Hydrogen

$$E_s = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{v,X} + h \quad (7)$$

$$E_s^o = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{v,X} + h \quad (8)$$

$$\log\left(\frac{k_X}{k_H}\right) = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{v,X} + h \quad (9)$$

$\alpha, \beta, \psi =$ susceptibility constants; $h =$ constant

Figure 8. The extended Hammett equation (5). Charton's modification (6) including a parameter characteristic of the proximity effect of a substituent (ζ) this was later defined as the van der Waals radii, relative to Hydrogen ($r_{v,H}$). Equations 7 and 8 were used by Charton to correlate Taft's steric parameters.

Another widely used multi-parameter LFER was developed by Fujita and Nishioka.[83] This relationship can be used for the comparison of *ortho, meta* and *para* mono- or poly-substituted arenes by accounting for the separate polar and steric effects of a substituent (Figure 9, equation 11). In this relationship the total polar effect is expressed in terms of the In the Fujita-Nishioka relationship, the total polar effect of a substituent is expressed in terms of the "ordinary" and the "proximity" electrical effects. The "ordinary polar effect" is expressed using the pre-defined *σ* (Hammett) constant; in the case of *ortho*-substitutents, it is tentatively defined as being equal to that of *para* substituents (Figure 9, equation 10). This assumption can underestimate inductive effects whilst over-estimating the mesomeric effects of a ring-substituent; thus for substituents in *ortho*, the field constant *F* is included as a measure of the substituent's "proximity polar effect" in attempt to account for these discrepancies. This proximity effect is factored solely by the corrected Swain Lupton constant (*F*) and is defined as an overlapping effect in addition to the ordinary polar effect regardless of whether this arises through the *σ*-bond network or more directly by a field effect.[84,85] The resonance effect is not involved in this proximity factor, and as a result the addition of this term is regarded as a correction for the under and over-estimation detailed above. Lastly, the steric term E_S^c is solely a space filling factor of the substituent calculated by Kutter and Hansch as a function of the van der Waals radius and corroborated against Taft's E_s values.[77]

$$\textit{assuming}: \sigma_o \equiv \sigma_p \quad (10)$$

$$\log\left(\frac{k_{o,m,p}}{k_{ref}}\right) = \rho\sigma_{o,m,p} + \delta E_s^{c,ortho} + fF_{ortho} + c \quad (11)$$

$$\rho, \delta, f = \text{susceptibility constants};\ c = \text{constant}$$

Figure 9. The Fujita-Nishioka equation (11). The relationship can be used for the analysis of a set of data containing *ortho, meta* and/or *para*-substituted arenes by taking into account the "ordinary polar effect" (respective *σ* constant), "proximity polar" effect (corrected field constant *F*) and the corrected Taft steric constant (E_s).

1.8.2. – Application of the Fujita-Nishioka equation

The Fujita-Nishioka equation seemed the most suitable relationship to apply to our data as it can be used to analyse the electronic and steric effects of a dataset containing mono- or poly- *ortho, meta* and *para* substituted substrates. Consequently, the steric and electronic parameters for all thirteen acids studied experimentally were compiled (Table 4),[83] and the susceptibility constants ρ, δ and f were determined using multiple linear regression (Table 5). A good correlation was found with both the experimental (Figure 10, r = 0.89) and theoretical reactivity data (Figure 11, BP, r = 0.91). Direct comparison of the susceptibility constants in Table 5 indicates that all three data sets agree on the significance of the parameters as indicated by the sign of the constants. The experimental and M06 theoretical data produce constants of similar magnitude, while the BP theoretical data produces slightly different constants albeit with the same implication and an excellent correlation to the model. The sign of the parameters indicates that polar effects ($\rho\sigma$ and fF) offer a rate enhancement while an overall negative δE_s suggests that bulky groups retard the reaction rate. With respect to the factors determining the *ortho* effect (fF and δEs) it can be understood that a combination of low steric and high 'proximity' polar effects are the most important factors in promoting decarboxylation for *ortho* substituted benzoic acids.

Table 4. Data correlation of the theoretical and experimental reaction rates for all benzoic acids tested using the Fujita-Nishioka equation.

Entry	R[a]	$\ln\frac{k_x}{k_{CF3}}$ (exp.)	$\ln\frac{k_x}{k_{CF3}}$ (theo)[b]	$\sigma_{o,m,p}$[c,d,e]	E_s[c d,e]	F[d,e]
1	*o*-F+*m*-NO_2	4.35	4.13	0.77	−0.46	0.43
2	*o*-NO_2	3.93	2.79	0.76	−1.01[f]	0.67
3	*o*-Cl+*m*-NO_2	3.76	4.40	0.94	−0.97	0.43
4	*o*-Br+*m*-NO_2	3.66	3.08	0.94	−1.16	0.44
5	*o*-Me+*o*-NO_2	3.52	1.16	0.59	−2.25	0.63
6	*o*-F	2.89	1.08	0.06	−0.46	0.43
7	*o*-Br	2.03	1.43	0.23	−1.16	0.44
8	*o*-Cl	1.81	−0.13	0.23	−0.97	0.41
9	*o*-Cl+*o*-Me	1.63	−2.51	0.06	−2.21	0.37
10	*o*-OEt	1.41	0.29	−0.24	−0.55	0.26
11	*o*-OMe	1.41	−1.45	−0.27	−0.55	0.22
12	*o*-O^{i}Pr	1.35	0.87	−0.45	−0.55	0.30
13	*o*-CF_3	0.00	0.00	0.54	−2.45	0.38

[a]The compounds are ranked according to the logarithmic experimentally calculated relative rate. [b]Derived by applying the Eyring equation at 120 °C (393 K) to the data calculated using BP/TZP. [c]Assuming $\sigma_o = \sigma_{p.}$ [d]From references [83,85,86]. [e]Parameters for di-substituted acids were calculated additively see ref [87] for precedent. [f]From the minimum perpendicular dimension of the NO_2 group.

Table 5. Multi-linear regression analysis of the Fujita-Nishioka model for the experimental and theoretical relative rates of decarboxylation for the thirteen acids detailed in Table 4.[a]

Data Set	r	c	ρ	δ	f
Exp.	0.89	0.99	1.37	1.05	5.28
Theo. (BP)	0.91	1.41	3.59	1.71	1.32
Theo. (M06)	0.73	−0.41	1.67	1.37	6.32

[a]All models are statistically significant at a p value of 0.01, except M06 which yields a p value of 0.066.

The case of *o*-CF_3 (Table 4, entry 13) exemplifies the ambivalent behaviour of the steric factor. As mentioned previously, the large and electron-withdrawing CF_3 greatly destabilises the starting structure (**CP3**) of the *ortho* isomer compared to the *para* (+6.9 kcal mol^{-1}). However, the electron-withdrawing nature of the substituent fails to stabilise the transition state structure, as any beneficial electronic effect seems to be offset by negative steric influence; resulting in a **TS** destabilisation of +1.6 kcal mol^{-1} (*ortho*−*para*), an absolute activation barrier of 25.2 kcal mol^{-1} and the lowest relative rate out of the substrates tested in this study. Unfortunately, the dichotomy of the steric effects in this system cannot be easily accounted by the Fujita-Nishioka model as one set of steric parameters is defined for the reaction as a whole, however it is evident here that sterics can have opposing contributions on the **CP3** and **TS** structures.

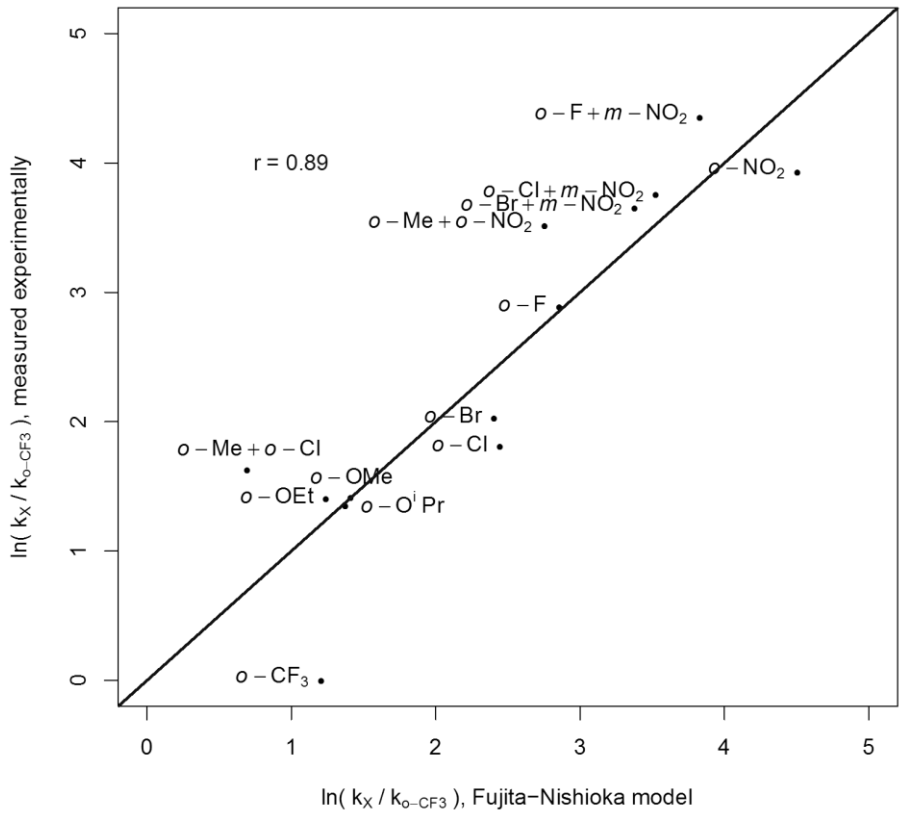


Figure 10. Plot of experimental logarithmic relative rates against the modified Fujita-Nishioka relationship (equation 11).

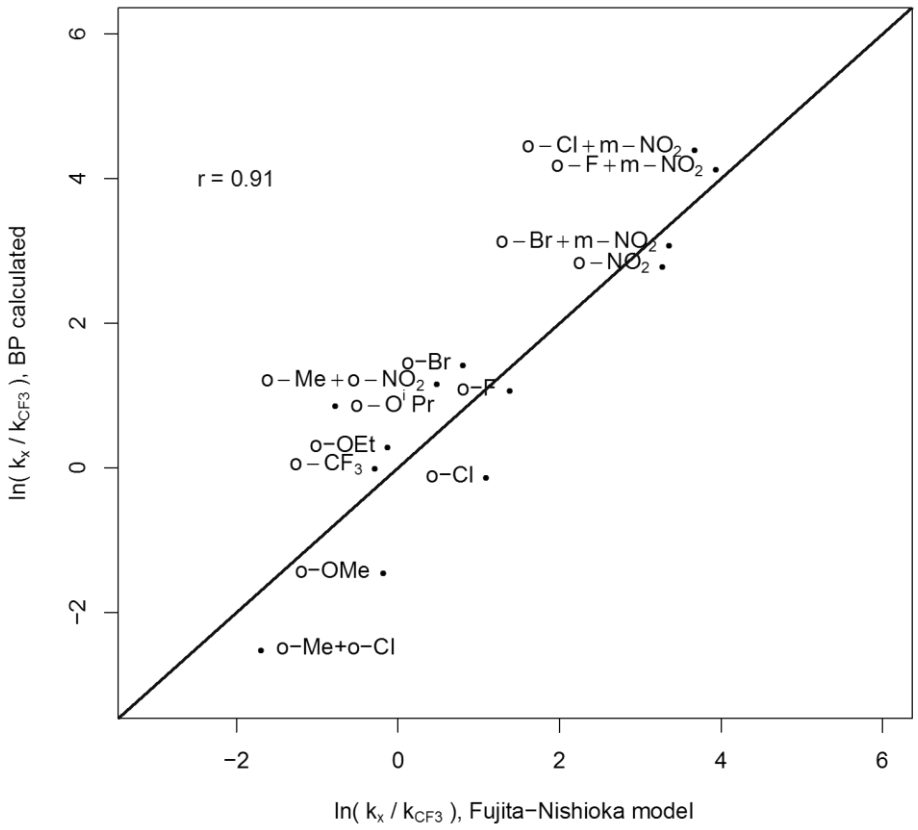


Figure 11. Plot of BP calculated logarithmic relative rates against the modified Fujita-Nishioka relationship (equation 11).

To probe the effect of further substitution on the ring we investigated the *ortho*-halogen series (F, Cl, Br) with the addition of a NO_2 group in *meta* to the carboxylic acid. The overall 'ordinary' polar coefficient (σ) of both substituents was calculated by addition of the individual parameters (Table 4, entries 1, 3, 4).[87] A good correlation was obtained for the three models with all resulting in an increased activation towards decarboxylation with the addition of an electron-withdrawing group in *meta* which is consistent with the positive $\rho\sigma$ term.

Next, the effect of a second substituent in the ortho position was investigated. The experimental and theoretical relative rate data for *ortho*-Cl+*ortho*-Me benzoic acid was obtained (Table 4, entry 9). Incorporation of the methyl group, which is both weakly electron-donating and sterically demanding, results in a decrease in the rate of decarboxylation compared to the mono *ortho*-Cl benzoic acid, as observed with both the experimental and theoretical data (Table 4, entry 7). Analysis of the polar and steric parameters for this acid reveals a significant increase of the steric parameter (E_s from −0.97 to −2.21) and a slight reduction of both polar components (σ from 0.23 to 0.06 and F from 0.41 to 0.37). Moreover, a similar decrease in reactivity also occurs in the case of *ortho*-Me+*ortho*-NO_2 benzoic acid (Table 4, entry 5). This additional *ortho*-Me group again resulted in a decrease in the experimental and theoretically calculated relative rates ($\ln k_{rel}$ (exp) from 3.93 to 3.52 and $\ln k_{rel}$ (theo) from 2.79 to 1.17; Table 4, cf. entries 2 and 5).

1.9. – CONCLUSIONS

In conclusion, we have presented a mechanistic study on the Ag-catalysed protodecarboxylation of *ortho*-substituted benzoic acids, which combines an experimental and computational approach, as well as the use of the Fujita-Nishioka linear free energy relationship.

Our computational studies corroborate previous reports[22] that the difference in activation energy of most *ortho*-substituted acids with respect to the other regioisomers is related to an inherent destabilisation of the structure of starting material. However, to lower the overall activation barrier the transition state structure must also be stabilised. When the transition state structure of the *ortho* isomer is compared to the *meta* and *para* isomers, the axial positioning of the groups on the *ipso* carbon largely precludes any steric hindrance that was present in the starting material. Nonetheless, this structural relief does not justify the reactivity variance observed for differently substituted *ortho* benzoic acids and this can only be accounted for when the electronic nature of the substituent is considered.

With the analysis of computational and kinetic data for specific cases, the electronic and steric influences have been delineated. Namely, for the case of the *ortho*-bromo and *ortho*-methyl benzoic acids, both have substituents which are similarly sized and thus afford a similar destabilisation of the starting material. However the electron-withdrawing bromine atom can stabilise the **TS** enough to lower the overall activation barrier; whereas the weakly electron-donating and sterically demanding methyl group destabilises the **TS** and concomitantly increases the overall barrier, resulting in no reaction under the standard conditions. Furthermore, for the case of the *ortho*-bromo and *ortho*-trifluoromethyl benzoic acids, both substituents have similar electronic properties but are of significantly different size. And, although the bulky *ortho*-CF_3 group destabilises the **CP3** structure, it also causes a significant destabilisation of the **TS** which actually works to counteract any beneficial electronic effects of the group. As a result of the size differentiation, there is stark difference in reaction rate for *ortho*-bromo and *ortho*-CF_3, despite being electronically similar.

The use of the Fujita-Nishioka linear free energy relationship showed an excellent correlation to both our computational and kinetic data and allowed for the separate analysis of steric and electronic effects. The implication of the susceptibility constants derived from the model indicate the importance of the electronic effect in addition to the negative role that steric bulk can play; but unfortunately the model could not account for the positive steric effects. Consequently, on consideration of the kinetic and computational data in addition to the LFER, the *ortho*-effect in this system can be outlined as a sterically driven destabilisation of the reactant in combination with a stabilisation of the transition state by electron-withdrawing substituents in addition to a steric destabilisation of the transition state for sizeable substituents.

1.10. – FUTURE OUTLOOK

The combined study discussed in this chapter has given valuable insight into the observed *ortho*-effect in the Ag-catalysed system. It has also shown that the addition of electron-withdrawing substituents in the *meta* or *para* position can drastically improve the rate of reaction by lowering the free energy of activation. Ideally the experimental model shown in Figure 10 could be utilised to predict the reactivity of an untested substrate. However, it only contains 13 examples and the dataset should be increased if the relationship were to be used as a predictive tool. This would require calculating the initial rates of several other substrates to strengthen the model, but this is time consuming. On the other hand, the DFT could be utilised to calculate the activation energies, and hence relative rates of untested substrates. However, there are notable discrepancies in the reactivity order predicted by both the BP and M06 functionals when compared to the experimental data (see Figures 10, 11 and S1-7). Analysis of the susceptibility constants generated from least squares analysis of the data and the Fujita-Nishioka equation (Table 5) shows that although the M06 data resulted in susceptibility constants close to those derived from the experimental data, the BP data gave a much better overall correlation and was consequently chosen. The difficulty in reaching agreement between experimental and theoretical data is due to intrinsic limitations of DFT[88] and the non-inclusion of some effects like explicit solvation. Furthermore the logarithmic relationship between the experimental rate and the activation energy necessitates that small changes in the rates are accompanied with changes in the activation energies that are out of the accuracy of the theoretical method. Hopefully with future improvements in DFT analysis or by finding a more appropriate functional, a more extensive model can be built.

As discussed in the introduction, the ability of Rh and Au to catalyse the decarboxylation of (hetero)aromatic acids has been recently discovered. However, an understanding of reactivity in these systems is limited. Catalytic protodecarboxylation by Au-NHC complexes[68] seem to tolerate a wider range of substrates than the Ag-catalysed system. Including substrates which are unreactive in the Ag/DMSO system; for example those which contain electron-rich and bulky substituents such as 2,4,6-trimethylbenzoic acid and *ortho*-NMe_2 benzoic acid. Furthermore, a range of non-*ortho* substituted acids are also tolerated at higher temperatures. Although the Au-NHC system is more expensive than the Ag/DMSO system, the reactions requires much lower loadings of catalyst (2 mol % compared to 20 mol %) and a quantitative treatment of the protodecarboxylation reaction, as carried out in this study, would give valuable insight into reactivity in this system.

The substrate scope of the Rh-catalysed decarboxylations reported by Zhao and co-workers[63,64] appear to be limited to fluoro and methoxy containing substrates, with one example of a heteroaromatic substrate. However, it is not clear if this is the extent of substrate scope or only

those which have been reported or tested. Miura and Satoh have shown that other substituents can be tolerated in the decarboxylative cyclisation to form naphthalenes[60] and carbazoles[61]. Due to the low catalyst loading and the opportunity to augment reactivity through ligand effects, the scope of the Rh-decarboxylation should be further investigated. In their initial paper[60] Miura and Satoh also reported that iridium complexes (in combination with an Ag oxidant) can afford much higher yields of naphthalene products, which occur through a decarboxylative pathway. For this transformation, the Ir-catalysed decarboxylation occurs at much lower temperatures than the Rh-system. However, iridium decarboxylative activation is considerably under investigated, perhaps due to cost, but nonetheless investigation of the substrate scope could open new avenues in decarboxylative transformations.

Chapter 1 – Supporting Information

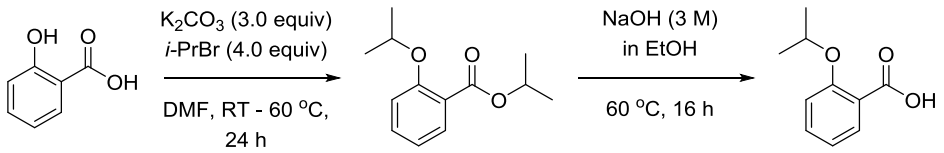
S1.1. – EXPERIMENTAL SECTION

S1.1.1. – General information

Unless otherwise stated all reactions were carried out under ambient atmosphere. Anhydrous DMSO, DMF and all other reagents were purchased from commercial suppliers and used without further purification. Silver carbonate was purchased from Acros. ^{1}H NMR spectra, recorded at 400 MHz are referenced to the residual solvent peak at 7.26 ppm ($CDCl_3$). For the protodecarboxylation rate studies the ^{1}H NMR spectra were recorded at 400 MHz (Bruker AV400 spectrometer) in a 3:2 ratio of $CDCl_3$ to h_6-DMSO, are referenced to an internal standard (mesitylene, 6.78 ppm; or 1,3,5-trimethoxybenzene (TMB), 6.08 ppm) for consistency as the $CHCl_3$ peak in DMSO solution has a variable resonance between 8.0 and 8.3 ppm. ^{13}C NMR spectra, recorded at 101 MHz and referenced to the residual solvent peak at 77.16 ppm.

S1.1.2. – Starting material preparation

2-Isopropoxybenzoic acid (21)[89]



21

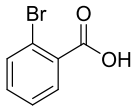
2-bromopropane (1.93 mL, 20.4 mmol) was added dropwise to a stirred suspension of salicylic acid (0.712 g, 5.1 mmol) and K_2CO_3 (2.12g, 15.3 mmol) in anhydrous DMF (13 mL), at room temperature, under nitrogen atmosphere. The suspension was then stirred at 60 °C for 24 h, and then the reaction mixture was cooled to room temperature, quenched with 10 mL water and evaporated to dryness. To the residue was added a 3 M solution of NaOH in EtOH (2.5 mL), the resulting slurry was stirred at 60 °C for 16 h. After this time the reaction mixture was cooled to room temperature and evaporated to dryness. The resulting residue was taken up in Et_2O, partitioned with H_2O (30 mL) and acidified to pH = 1 with conc. HCl, the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were washed with brine (1 x 90 mL) dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to afford **21** as an analytically pure yellowish oil (0.488 mg, 53% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (1H, br s), 8.20 (1H, dd, *J* = 1.6, 8.0 Hz), 7.54 (1H, td, *J* = 1.6, 8.8 Hz), 7.12 (1H, t, *J* = 7.6 Hz), 7.05 (1H, d, *J* = 8.4 Hz), 4.88 (1H, sept, *J* = 6.0 Hz), 1.49 (6H, d, *J* = 6.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) 165.6, 156.6, 135.0, 134.0, 122.4, 118.8, 114.2, 74.1, 22.2 (2C).

S1.1.3. – General procedure for the Ag-catalysed decarboxylation of benzoic acids

A mixture of benzoic acid (1.0 mmol), Ag_2CO_3 (27.6 mg, 0.01 mmol) in anhydrous DMSO (5.0 mL) were stirred for the allotted time at 120 °C, in a sealed vessel. After this time, 100 µL (0.2 M) of the solution was removed and quenched in solution the internal standard in 0.5 mL $CDCl_3$ solution (0.013 M) and the absolute concentration of unreacted starting material calculated by determining the relative ratio of unreacted starting material to product by integration of the product and starting material peaks, using ^{1}H NMR. The internal standard was added as an internal reference as the residual $CHCl_3$ peak can shift up to 8.32 ppm in the presence of DMSO.

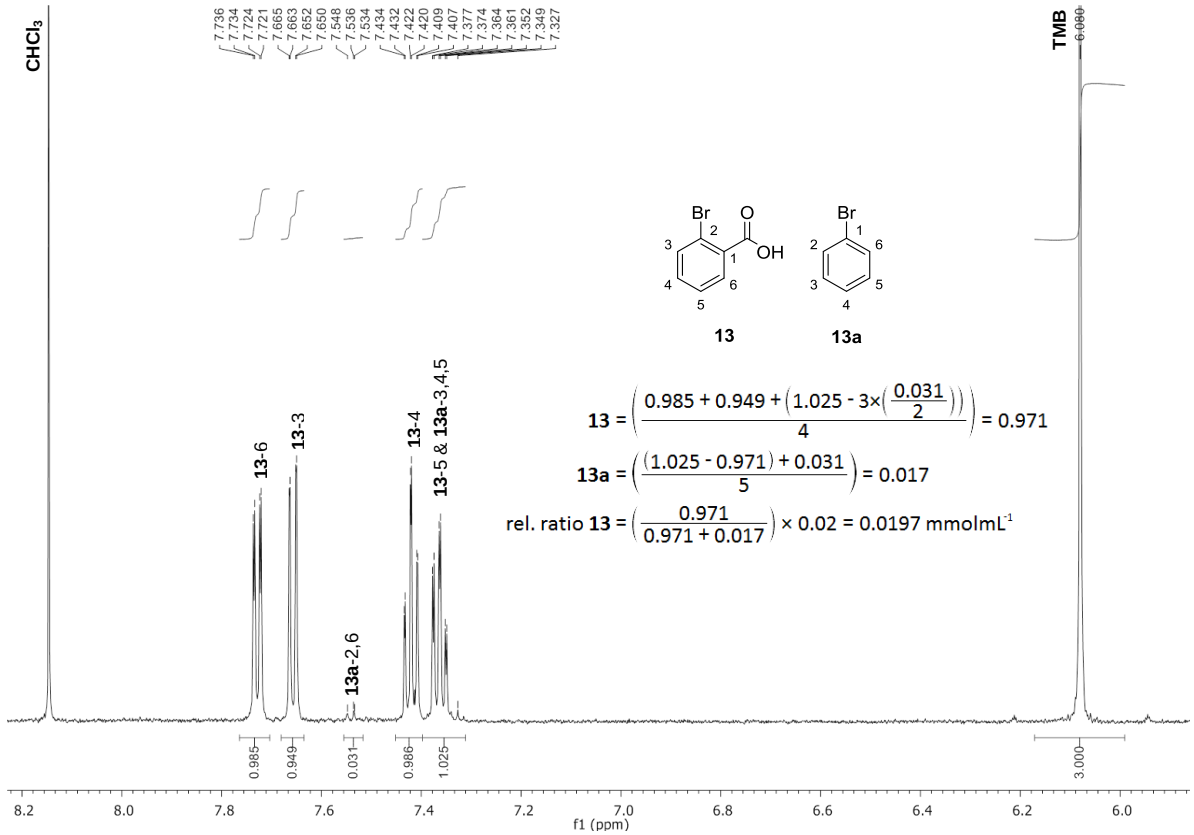
S1.1.4. – Spectroscopic data

2-Bromobenzoic acid (13)

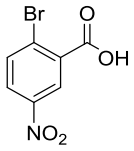


13

The reaction was carried out following the general procedure with **13** (0.201 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product **13a** and unreacted **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.66 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.42 (td, *J* = 1.1, 7.2, 7.6 Hz, 1H), 7.37 (td, *J* = 2.0, 7.6 Hz, 1H).

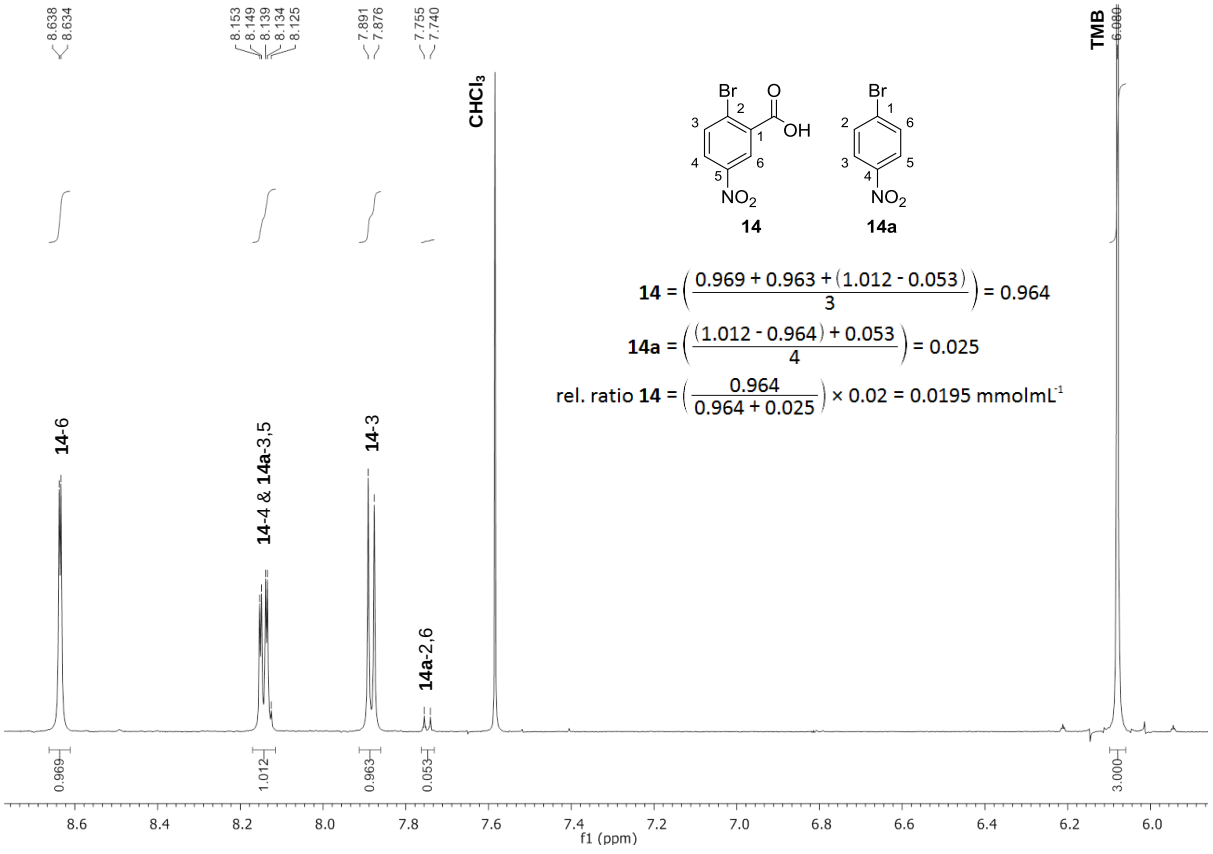


2-Bromo-5-nitrobenzoic acid (14)

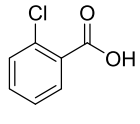


14

The reaction was carried out following the general procedure with **14** (0.246 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**14a**) and unreacted **14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.8 Hz, 1H), 8.20 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.96 (d, *J* = 8.8, 1H).



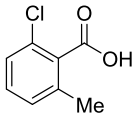
2-Chlorobenzoic acid (15)



15

The reaction was carried out following the general procedure with **15** (0.157 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**15a**) and unreacted **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.45-7.47 (m, 2H), 7.66-7.70 (m, 2H). 7.35-7.39 (m, 1H).

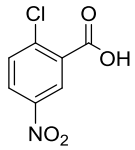
2-Chloro-6-methylbenzoic acid (16)



16

The reaction was carried out with **16** (0.051 g, 0.3 mmol), Ag_2CO_3 (8.3 mg, 0.03 mmol) in anhydrous DMSO (1.5 mL) was stirred for the allotted time at 120 °C in a sealed vessel. After this time the reaction was cooled rapidly in a dry ice-acetone bath and the crude dissolved in Et_2O (10 mL) and partitioned with $NaHCO_3$ (10 mL). The aqueous layer was separated, acidified with 1M HCl (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were washed with brine (20 mL) and dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The amount of unreacted **16** was calculated using 1,3,5-trimethoxybenzene as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.25 (m, 2H), 7.09-7.14 (m, 1H), 2.16 (s, 3H).

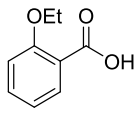
2-Chloro-5-nitrobenzoic acid (17)



17

The reaction was carried out following the general procedure with **17** (0.202 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**17a**) and unreacted **17**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.8 Hz, 1H), 8.30 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H).

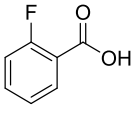
2-Ethoxybenzoic acid (18)



18

The reaction was carried out following the general procedure with **18** (0.166 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**18a**) and unreacted **18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.44 (ddd, *J* = 1.8, 7.6, 8.4 Hz, 1H), 7.04 (dd, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 1.6, 7.4 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H).

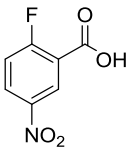
2-Fluorobenzoic acid (19)



19

The reaction was carried out following the general procedure with **19** (0.140 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**19a**) and unreacted **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.56 (m, 1H), 7.25 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.20 (ddd, *J* = 0.9, 8.3, 10.8 Hz, 1H).

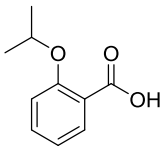
2-Fluoro-5-nitrobenzoic acid (20)



20

The reaction was carried out following the general procedure with **20** (0.185 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**20a**) and unreacted **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 2.9, 6.3 Hz, 1H), 8.44 (ddd, *J* = 3.2, 3.7, 9.1 Hz, 1H), 7.48 (t, *J* = 9.2, 1H).

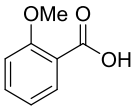
2-Isopropoxybenzoic acid (21)



21

The reaction was carried out following the general procedure with **21** (0.180 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**21a**) and unreacted **21**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.54 (td, *J* = 1.6, 8.8 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.88 (sept, *J* = 6.0 Hz, 1H), 1.49 (d, *J* = 6.0 Hz, 6H).

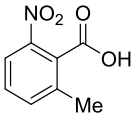
2-Methoxybenzoic acid (22)



22a

The reaction was carried out following the general procedure with **22** (0.152 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product **22a** and unreacted **22**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.47 (ddd, *J* = 1.6, 8.4 Hz, 1H), 7.06 (d, *J* = 8.3, 1H), 6.99 (app td, *J* = 0.8, 7.4 Hz, 1H), 3.89 (s, 3H).

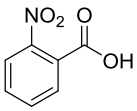
2-Methyl-6-nitrobenzoic acid (23)



23a

The reaction was carried out following the general procedure with **23** (0.181 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product **23a** and unreacted **23**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H).

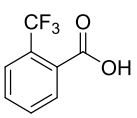
2-Nitrobenzoic acid (24)



24a

The reaction was carried out following the general procedure with **24** (0.167 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**24a**) and unreacted **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H,), 7.73 (app td, *J* = 1.6, 7.6 Hz, 1H), 7.68 (app td, *J* = 1.6, 7.6 Hz, 1H).

2-(Trifluoromethyl)benzoic acid (25)

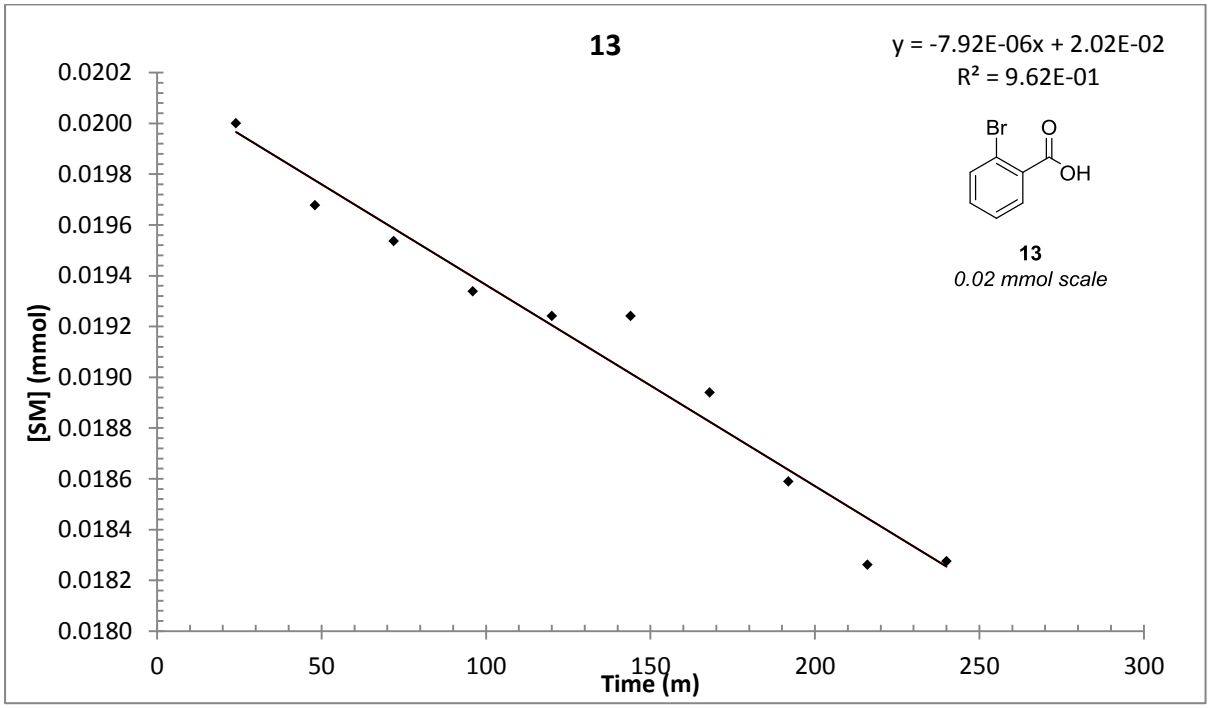


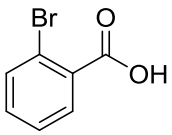
25a

The reaction was carried out following the general procedure with **25** (0.190 g, 1.0 mmol) to afford a mixture of the corresponding decarboxylated product (**25a**) and unreacted **25**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.8 Hz, 1H), 7.78 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.65-7.72 (m, 2H).

S1.1.5. – Kinetic data – Initial rates

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
13	24	96.6	0.0	1.000	0.0200
13	48	97.5	1.6	0.984	0.0197
13	72	92.6	2.2	0.977	0.0195
13	96	93.5	3.2	0.967	0.0193
13	120	91.3	3.6	0.962	0.0192
13	144	88.7	3.5	0.962	0.0192
13	168	87.5	4.9	0.947	0.0189
13	192	89.6	6.8	0.929	0.0186
13	216	91.4	8.7	0.913	0.0183
13	240	86.9	8.2	0.914	0.0183



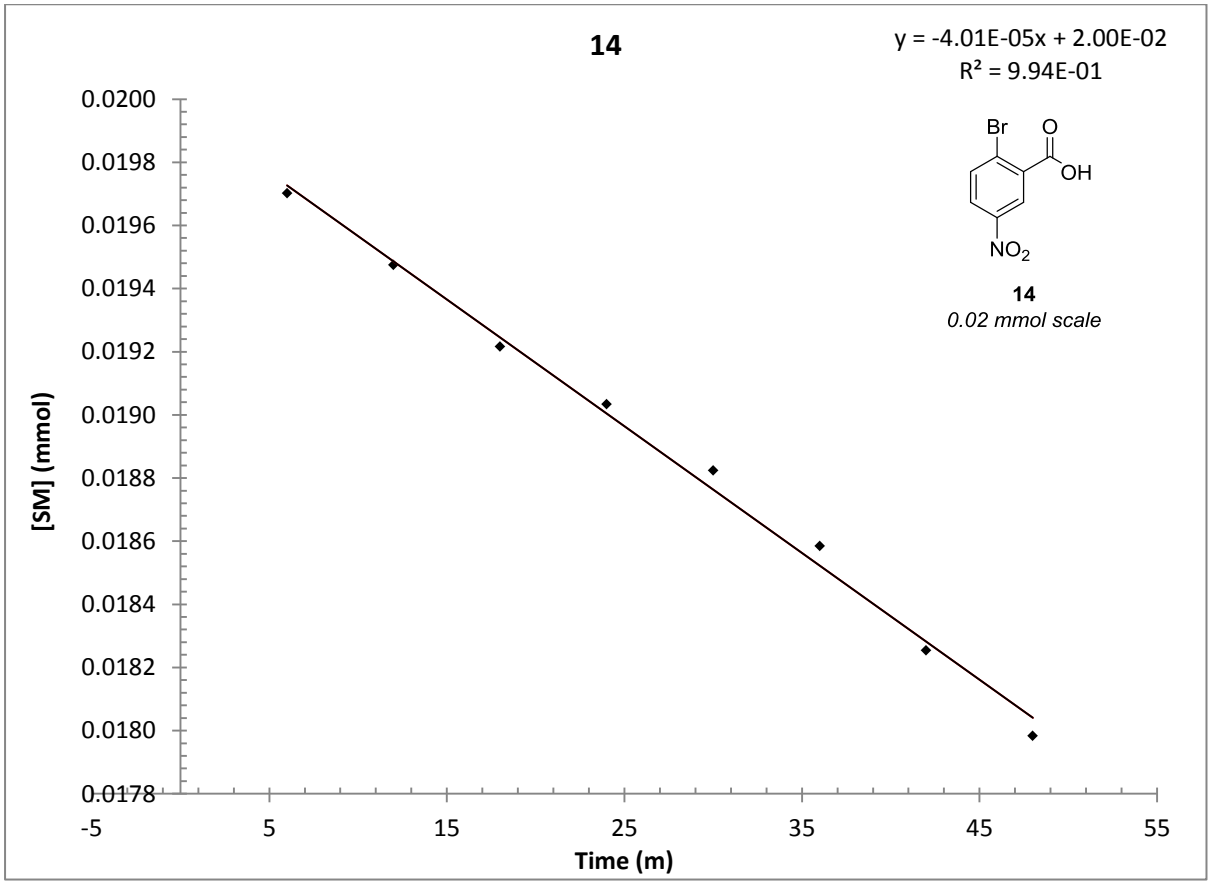


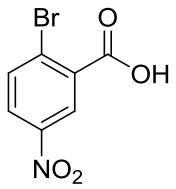
13

$\Delta G^{\neq}_{(\mathbf{13})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.59 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{13})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –1.20 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1)}$
14	6	99.0	1.5	0.985	0.0197
14	12	96.4	2.6	0.974	0.0195
14	18	93.2	3.8	0.961	0.0192
14	24	92.6	4.7	0.952	0.0190
14	30	91.2	5.7	0.941	0.0188
14	36	90.6	6.9	0.929	0.0186
14	42	86.8	8.3	0.913	0.0183
14	48	86.5	9.7	0.899	0.0180



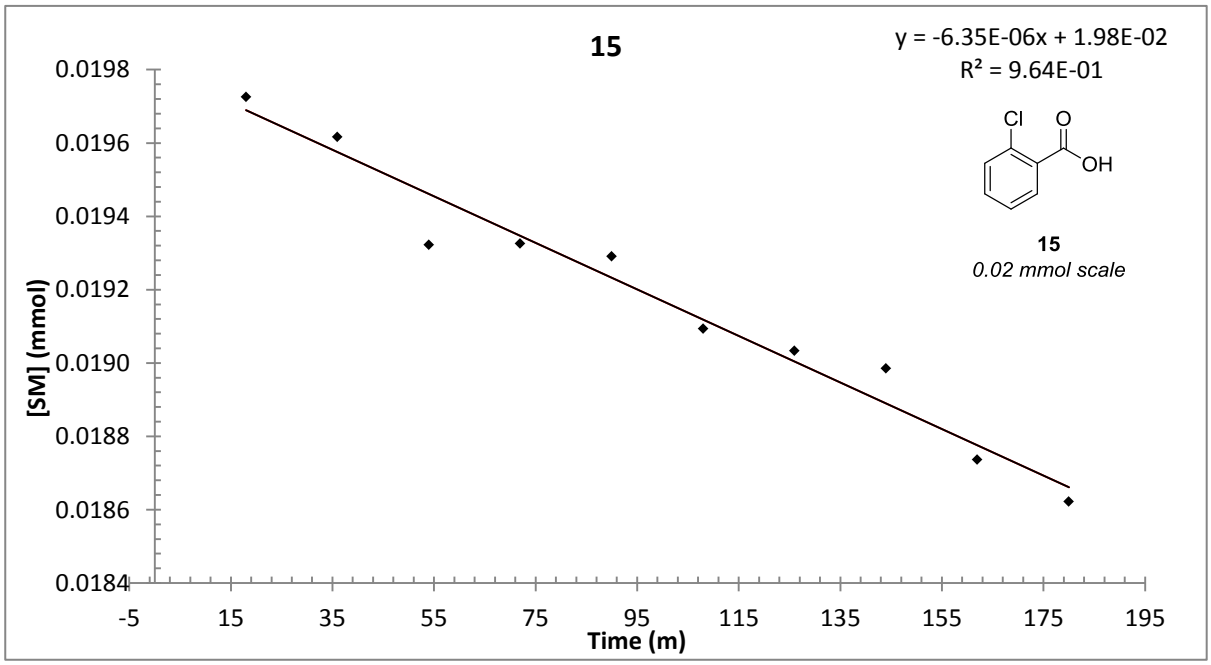


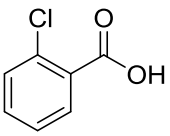
14

$\Delta G^{\neq}_{(\mathbf{14})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –2.85 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{14})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –2.41 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
15	18	93.4	1.3	0.986	0.0197
15	36	92.1	1.8	0.981	0.0196
15	54	91.2	3.2	0.966	0.0193
15	72	91.8	3.2	0.966	0.0193
15	90	89.8	3.3	0.965	0.0193
15	108	88.5	4.2	0.955	0.0191
15	126	90.6	4.6	0.952	0.0190
15	144	89.8	4.8	0.949	0.0190
15	162	89.0	6.0	0.937	0.0187
15	180	89.2	6.6	0.931	0.0186





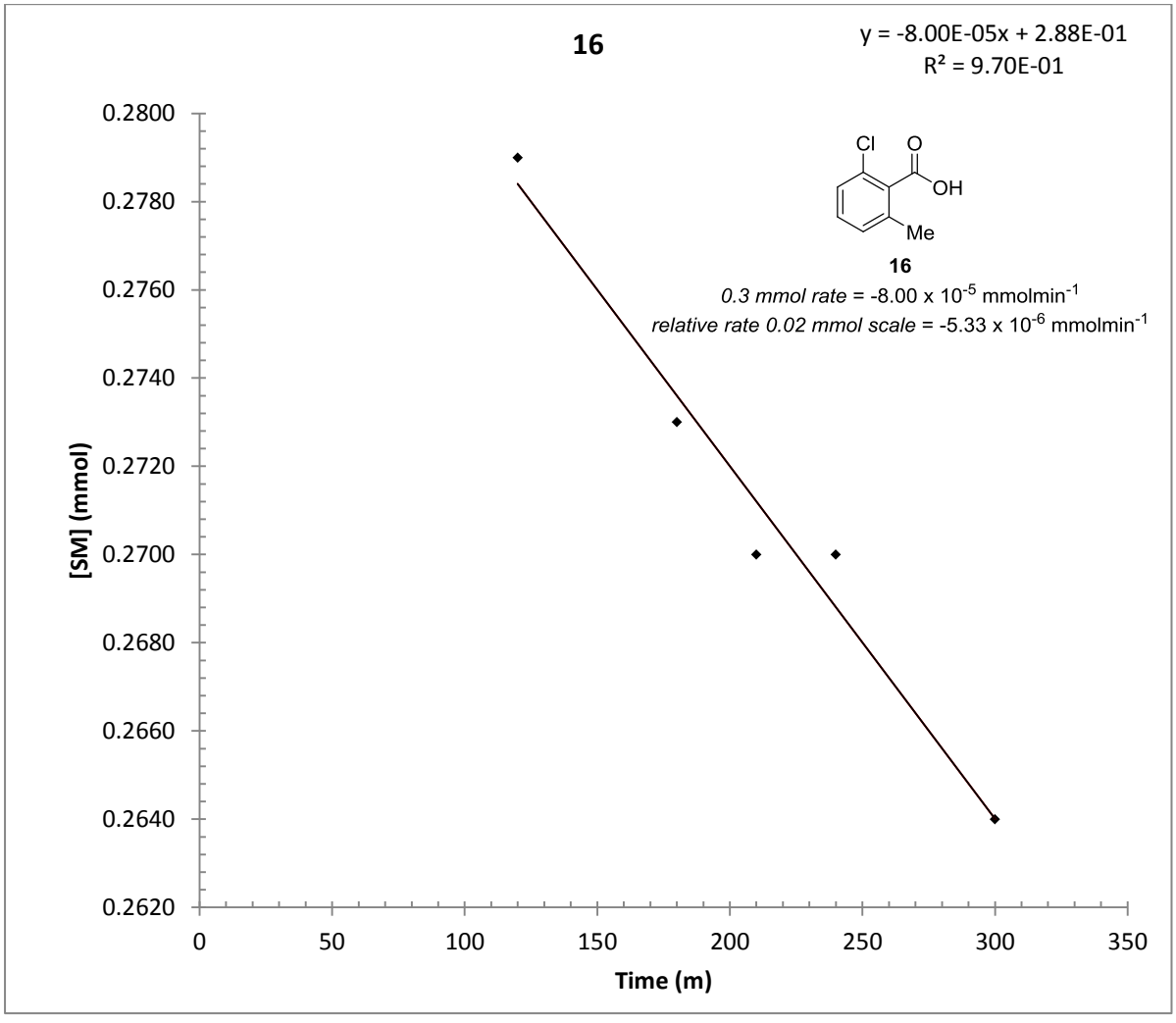
15

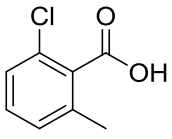
$\Delta G^{\neq}_{(\mathbf{15})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.41 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{15})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = 0.10 kcal mol^{-1}

Substrate	Time (m)	SM (%)	[SM][a] ($mmolmL^{-1}$)	[SM][b] ($mmolmL^{-1}$)
16	18	93	0.2790	0.0186
16	36	91	0.2730	0.0182
16	54	90	0.2700	0.0180
16	72	90	0.2700	0.0180
16	180	88	0.2640	0.0176

[a] 0.3 mmol scale reaction. [b] concentration relative to 0.02 mmol scale reaction



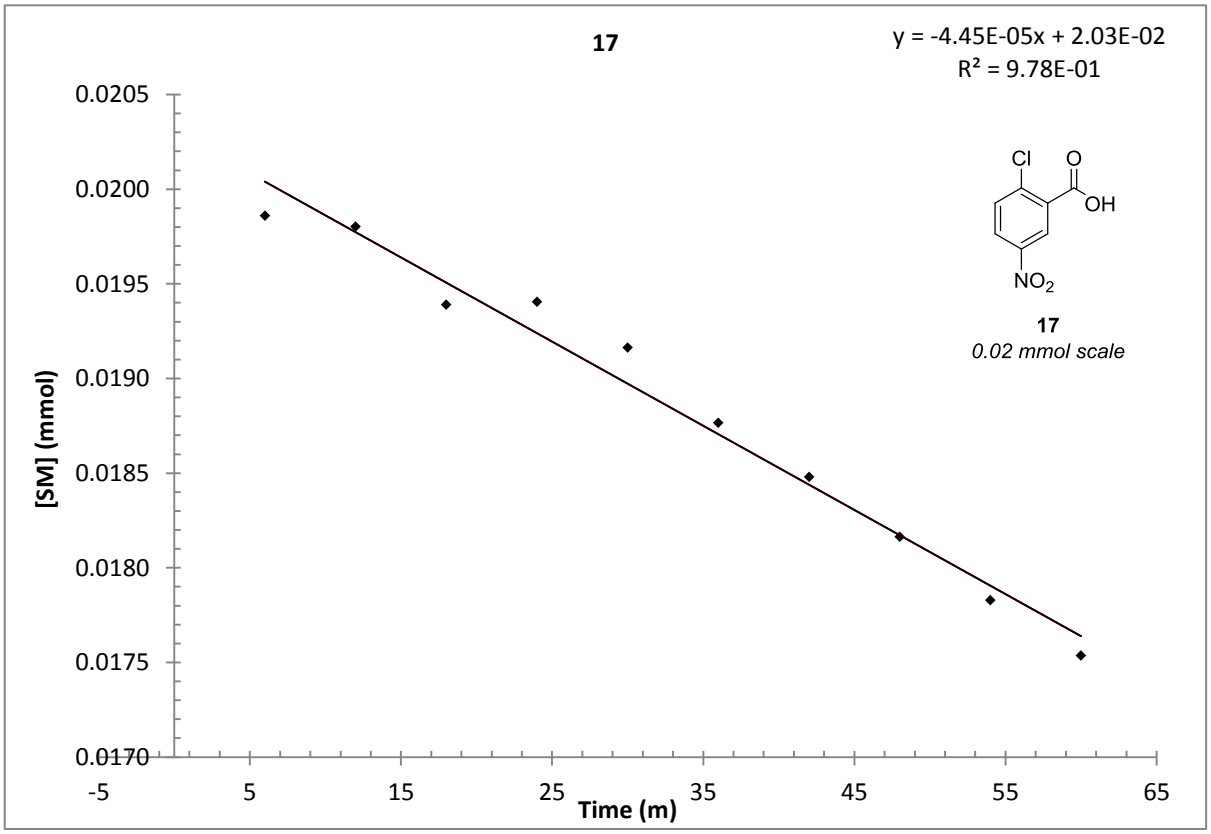


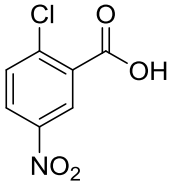
16

$\Delta G^{\neq}_{(16)} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.28 kcal mol^{-1}

$\Delta G^{\neq}_{(16)} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = 1.96 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
17	6	99.6	0.7	0.993	0.0199
17	12	100.6	1.0	0.990	0.0198
17	18	98.5	3.1	0.969	0.0194
17	24	94.7	2.9	0.970	0.0194
17	30	96.1	4.2	0.958	0.0192
17	36	92.7	6.1	0.938	0.0188
17	42	92.4	7.6	0.924	0.0185
17	48	89.0	9.0	0.908	0.0182
17	54	87.9	10.7	0.891	0.0178
17	60	85.4	12.0	0.877	0.0175



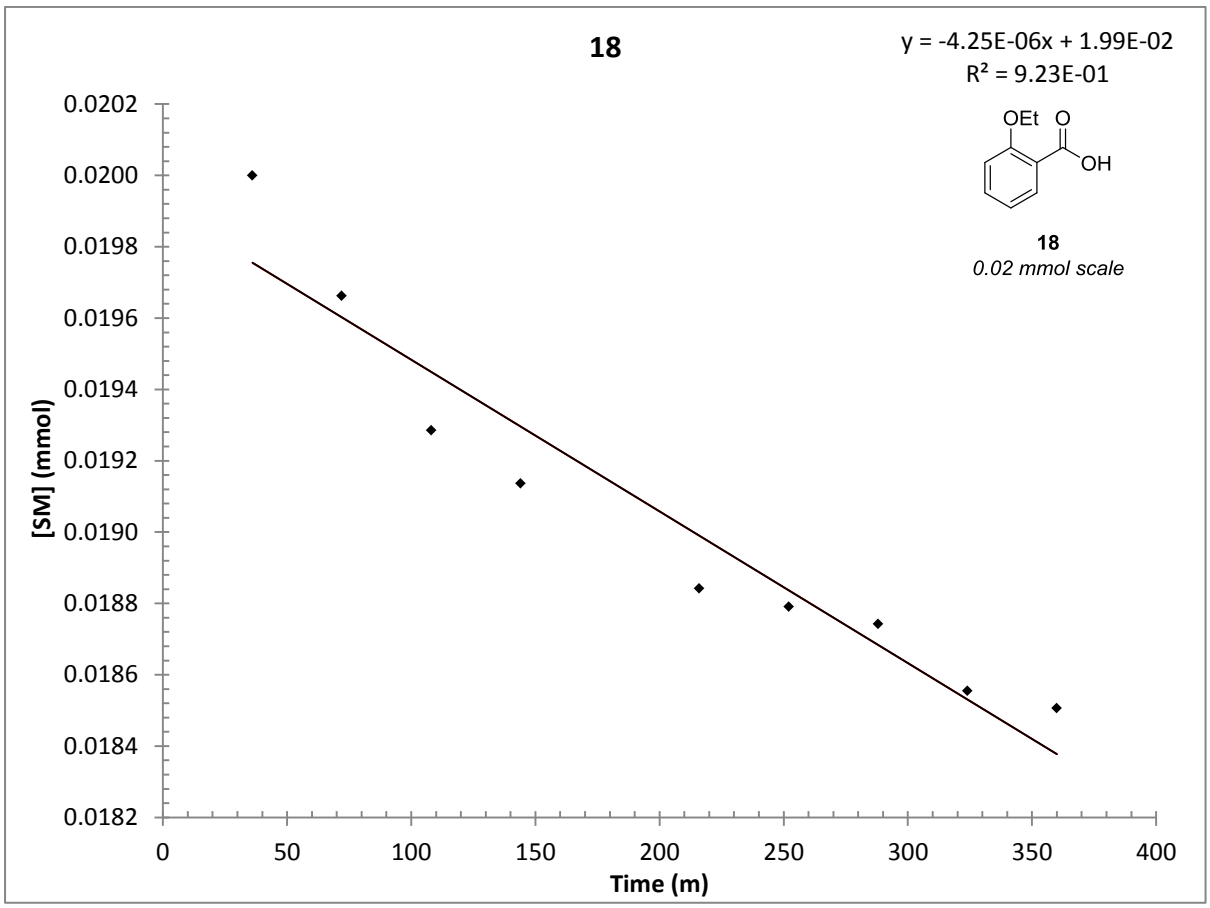


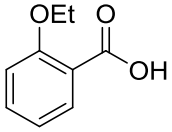
17

$\Delta G^{\neq}_{(17)} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –2.93 kcal mol^{-1}

$\Delta G^{\neq}_{(17)} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –3.44 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
18	36	100.4	0.0	1.000	0.0200
18	72	99.0	1.7	0.983	0.0197
18	108	97.1	3.6	0.964	0.0193
18	144	84.2	3.8	0.957	0.0191
18	216	84.6	5.2	0.942	0.0188
18	252	91.7	5.9	0.940	0.0188
18	288	89.4	6.0	0.937	0.0187
18	324	86.0	6.7	0.928	0.0186
18	360	89.2	7.2	0.925	0.0185



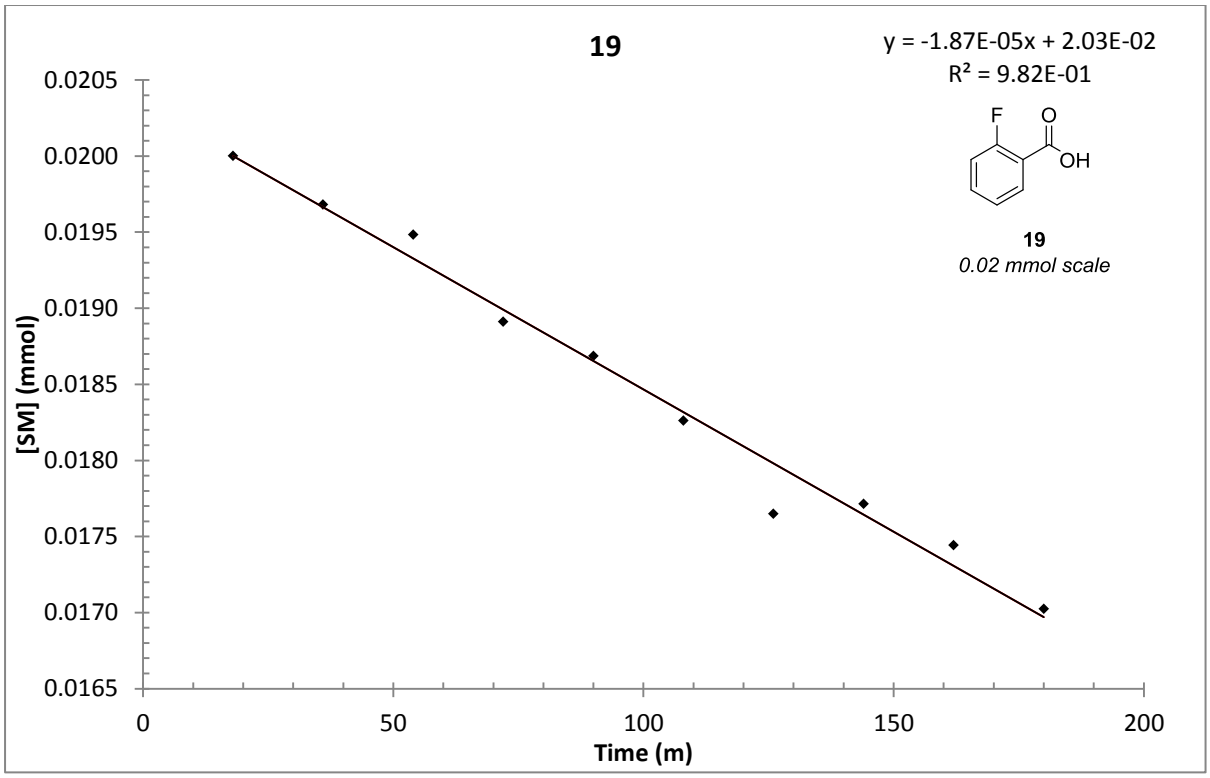


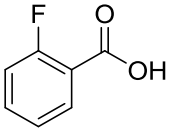
18

$\Delta G^{\neq}_{(18)} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.10 kcal mol^{-1}

$\Delta G^{\neq}_{(18)} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –0.23 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
19	18	95.8	0.0	1.000	0.0200
19	36	92.5	1.5	0.984	0.0197
19	54	90.5	2.4	0.974	0.0195
19	72	90.3	5.2	0.946	0.0189
19	90	88.1	6.2	0.934	0.0187
19	108	84.0	8.0	0.913	0.0183
19	126	84.8	11.3	0.882	0.0176
19	144	82.9	10.7	0.886	0.0177
19	162	80.5	11.8	0.872	0.0174
19	180	77.2	13.5	0.851	0.0170



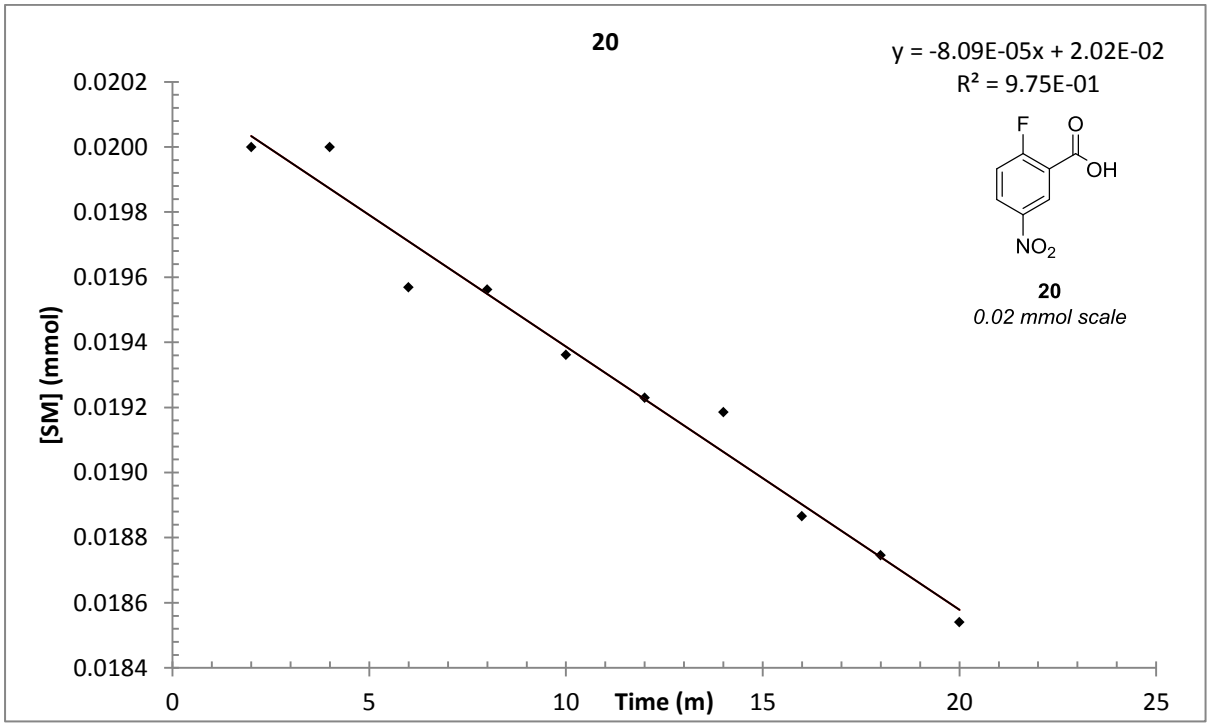


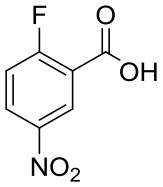
19

$\Delta G^{\neq}_{(\mathbf{19})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –2.26 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{19})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –0.84 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
20	2	95.5	0.0	1.000	0.0200
20	4	96.8	0.0	1.000	0.0200
20	6	95.4	2.1	0.978	0.0196
20	8	93.7	2.1	0.978	0.0196
20	10	94.0	3.1	0.968	0.0194
20	12	92.3	3.7	0.961	0.0192
20	14	89.5	3.8	0.959	0.0192
20	16	89.8	5.4	0.943	0.0189
20	18	89.7	6.0	0.937	0.0187
20	20	88.9	7.0	0.927	0.0185



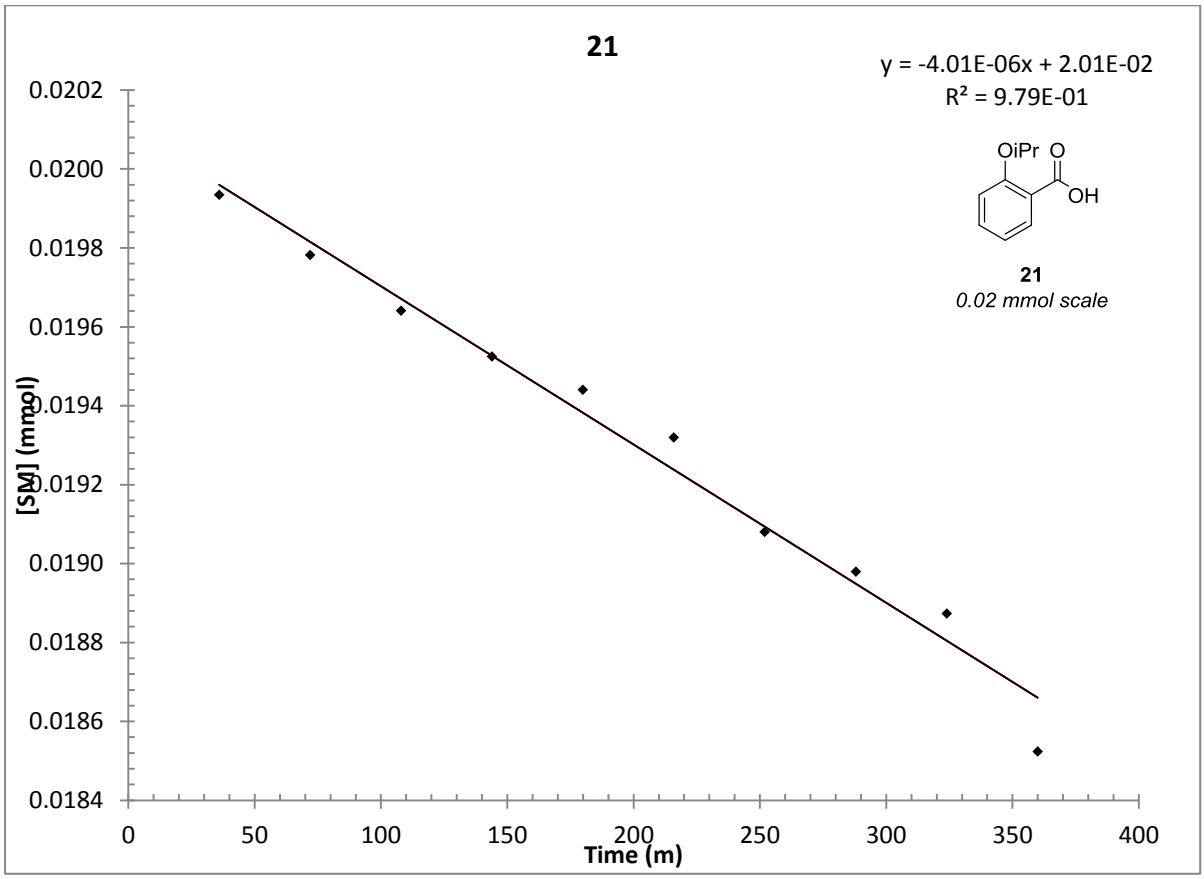


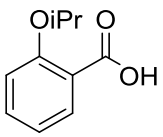
20

$\Delta G^{\neq}_{(\mathbf{20})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –3.40 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{20})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –3.23 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
21	36	91.5	0.3	0.997	0.0199
21	72	90.7	1.0	0.989	0.0198
21	108	92.9	1.7	0.982	0.0196
21	144	90.4	2.2	0.976	0.0195
21	180	90.3	2.6	0.972	0.0194
21	216	88.0	3.1	0.966	0.0193
21	252	87.1	4.2	0.954	0.0191
21	288	87.4	4.7	0.949	0.0190
21	324	85.4	5.1	0.944	0.0189
21	360	85.3	6.8	0.926	0.0185



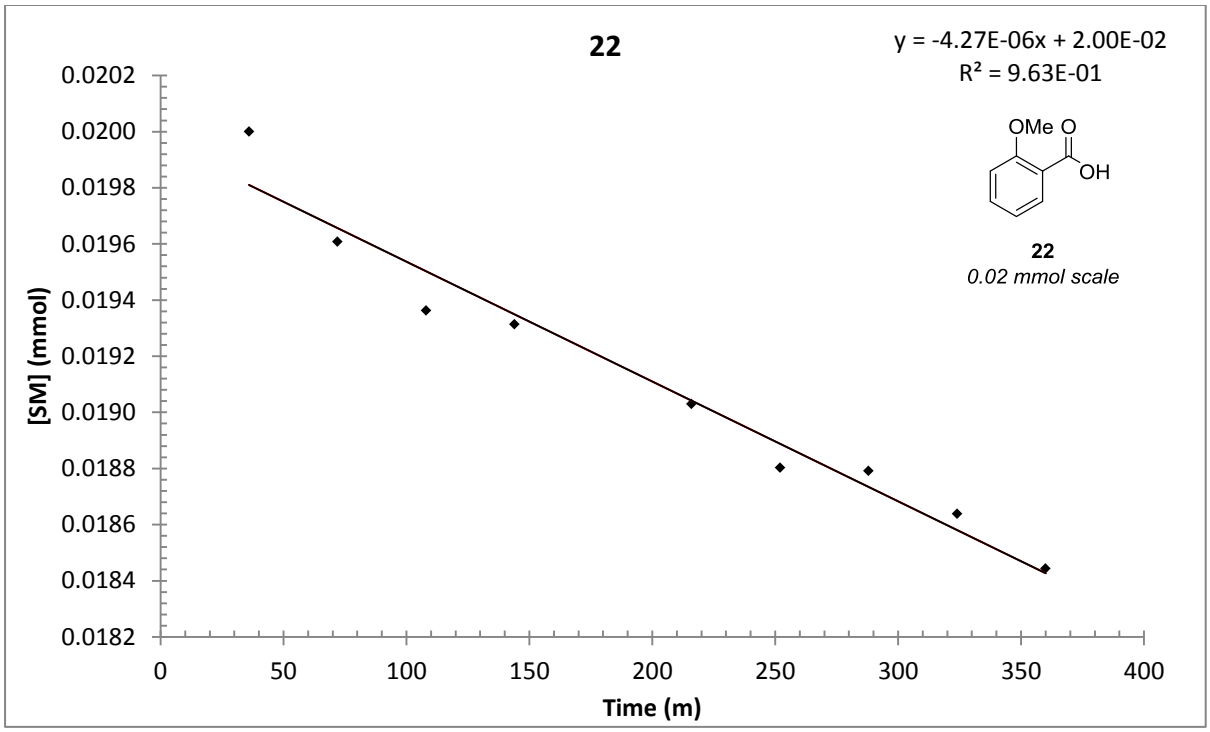


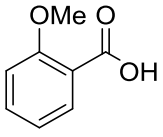
21

$\Delta G^{\neq}_{(21)} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.05 kcal mol^{-1}

$\Delta G^{\neq}_{(21)} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –0.68 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
22	36	107.0	0.0	1.000	0.0200
22	72	105.0	2.1	0.980	0.0196
22	108	103.3	3.4	0.968	0.0194
22	144	104.1	3.7	0.966	0.0193
22	216	102.0	5.2	0.951	0.0190
22	252	98.9	6.3	0.940	0.0188
22	288	101.0	6.5	0.940	0.0188
22	324	95.8	7.0	0.932	0.0186
22	360	96.0	8.1	0.922	0.0184



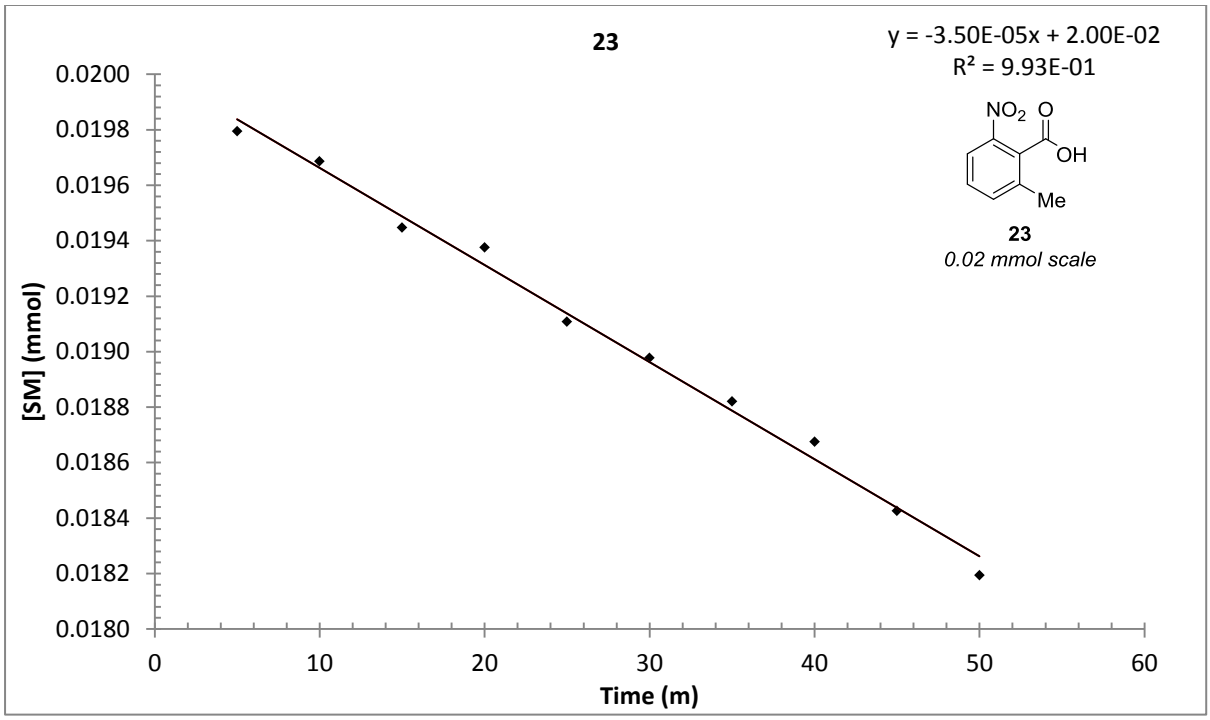


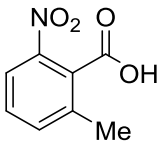
22

$\Delta G^{\neq}_{(\mathbf{22})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –1.10 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{22})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = 1.13 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
23	5	96.6	1.0	0.990	0.0198
23	10	94.0	1.5	0.984	0.0197
23	15	77.3	2.2	0.972	0.0194
23	20	93.0	3.0	0.969	0.0194
23	25	89.9	4.2	0.955	0.0191
23	30	92.8	5.0	0.949	0.0190
23	35	89.3	5.6	0.941	0.0188
23	40	90.2	6.4	0.934	0.0187
23	45	90.1	7.7	0.921	0.0184



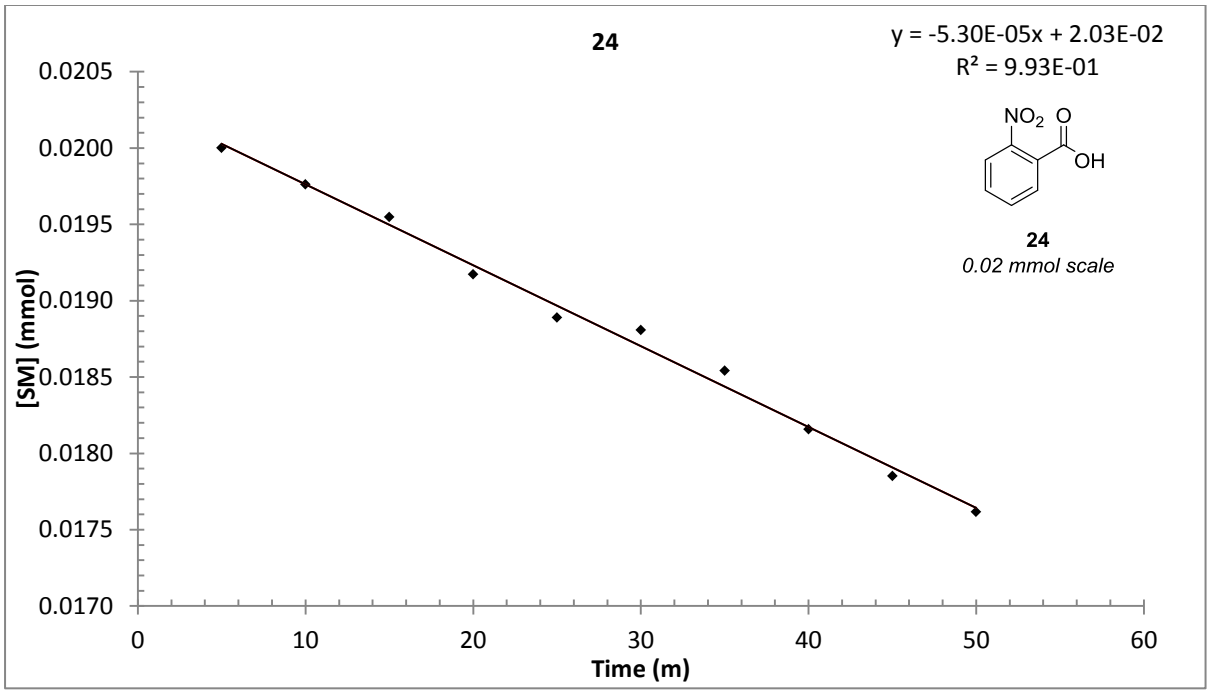


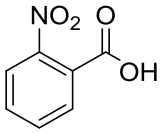
23

$\Delta G^{\neq}_{(\mathbf{23})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –2.75 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{23})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –0.91 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
24	5	84.1	0.0	1.000	0.0200
24	10	99.7	1.2	0.988	0.0198
24	15	99.4	2.3	0.977	0.0195
24	20	97.4	4.2	0.959	0.0192
24	25	93.5	5.5	0.944	0.0189
24	30	96.2	6.1	0.940	0.0188
24	35	90.3	7.1	0.927	0.0185
24	40	89.7	9.1	0.908	0.0182
24	45	89.7	10.8	0.893	0.0179



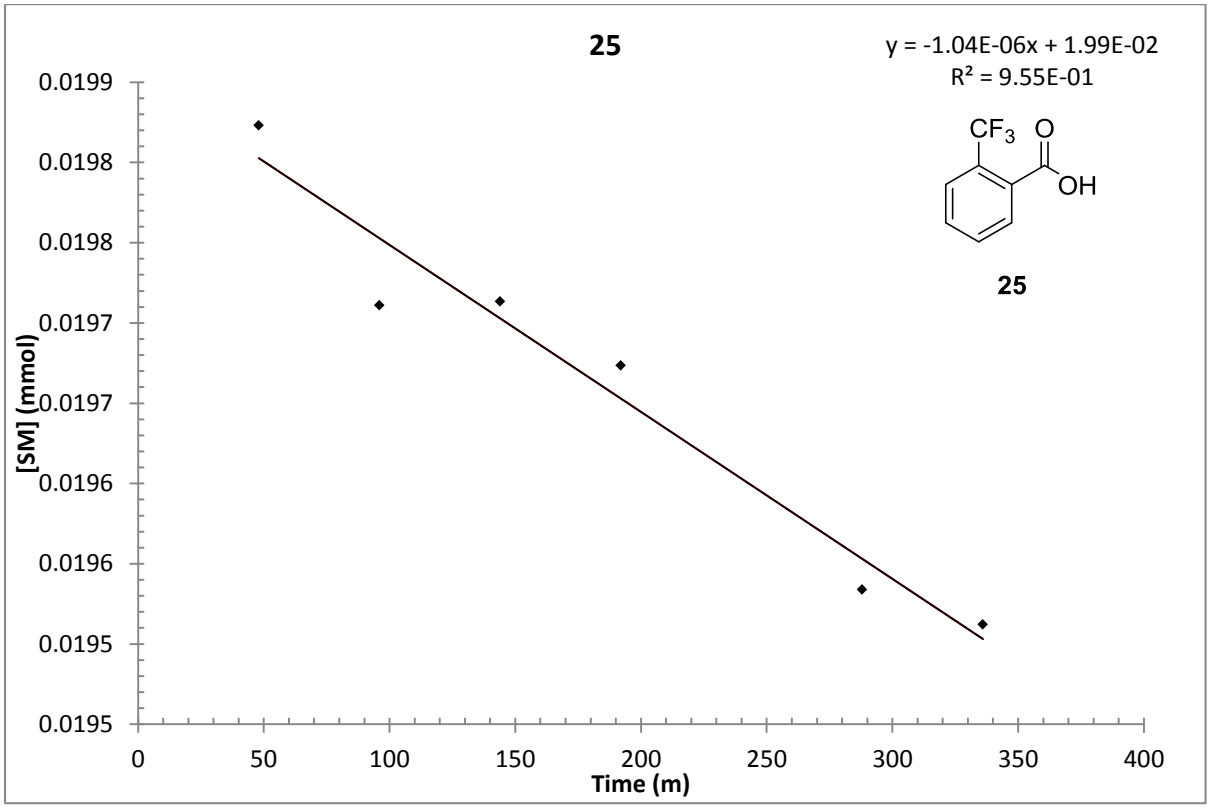


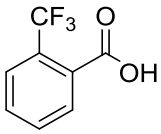
24

$\Delta G^{\neq}_{(\mathbf{24})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = –3.07 kcal mol^{-1}

$\Delta G^{\neq}_{(\mathbf{24})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = –2.18 kcal mol^{-1}

Substrate	Time (m)	SM (%)	H (%)	Rel. Ratio of SM	[SM] ($mmolmL^{-1}$)
25	48	95.3	0.9	0.991	0.0198
25	96	95.5	1.4	0.986	0.0197
25	144	96.3	1.4	0.986	0.0197
25	192	96.4	1.6	0.984	0.0197
25	288	96.4	2.3	0.977	0.0195
25	336	96.0	2.4	0.976	0.0195





25

$\Delta G^{\neq}_{(\mathbf{25})} - \Delta G^{\neq}_{(CF3)}$ (experimental) = 0.00 $kcalmol^{-1}$

$\Delta G^{\neq}_{(\mathbf{25})} - \Delta G^{\neq}_{(CF3)}$ (theoretical) = 0.00 $kcalmol^{-1}$

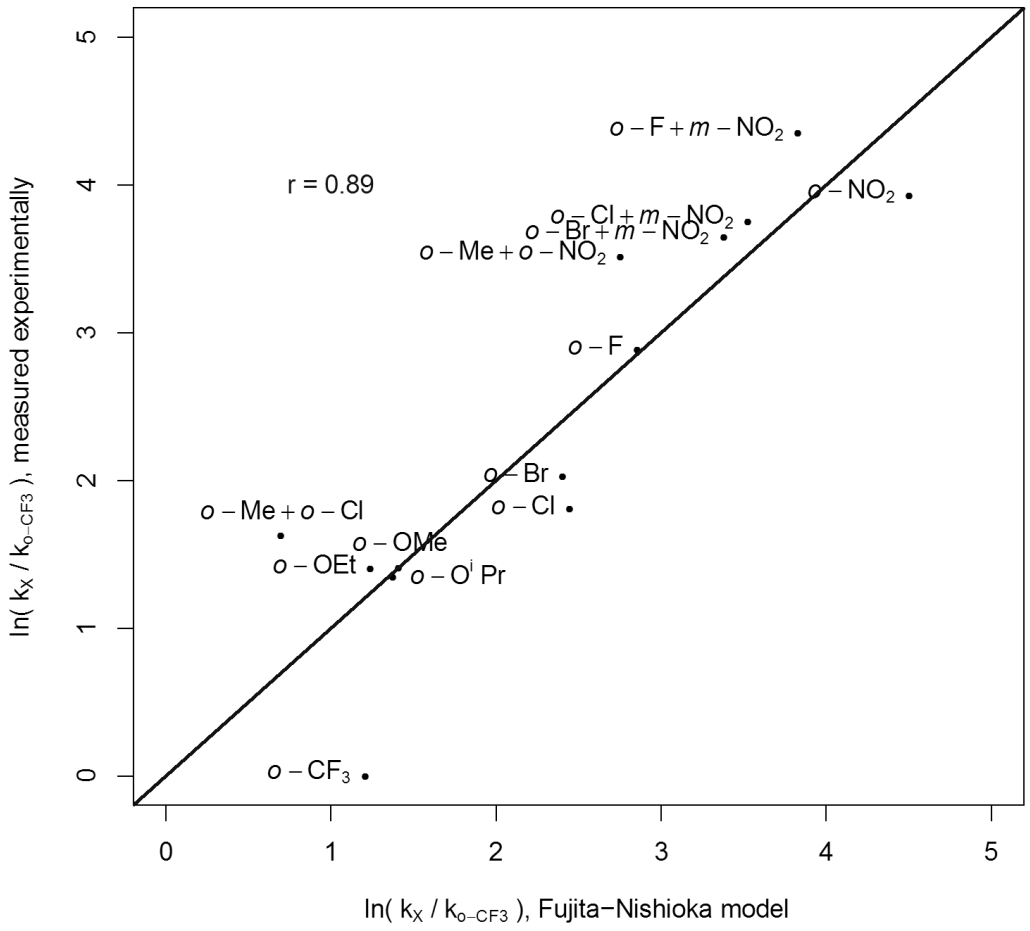
S1.1.6. – Regression analysis – LFER model

Table S1-1. Predefined parameters for all compounds used to build the Fujita-Nishioka model by multiple linear regression models.

Entry	Substituents[a]	$\ln \frac{k_x}{k_{CF_3}}_{exp}$	$\sigma_{o,m,p}$ [c,d,e]	$-E_s^{c,o}$ [d,e]	F [d,e]
1	*o*-F+*m*-NO_2	4.35	0.77	−0.46	0.43
2	*o*-NO_2	3.93	0.76	−1.01[f]	0.67
3	*o*-Cl+*m*-NO_2	3.76	0.94	−0.97	0.43
4	*o*-Br+*m*-NO_2	3.66	0.94	−1.16	0.44
5	*o*-NO_2+*o*-Me	3.52	0.59	−2.25[f]	0.63
6	*o*-F	2.89	0.06	−0.46	0.43
7	*o*-Br	2.03	0.23	−1.16	0.44
8	*o*-Cl	1.81	0.23	−0.97	0.41
9	*o*-Cl+*o*-Me	1.63	0.06	−2.21	0.37
10	*o*-OEt	1.41	-0.24	−0.55	0.22
11	*o*-OMe	1.41	-0.27	−0.55	0.26
12	*o*-O^{i}Pr	1.35	-0.45	−0.55	0.30
13	*o*-CF_3	0.00	0.54	−2.40	0.38

[a]The compounds are ranked according to the logarithmic experimentally calculated relative rate. [b]Derived by applying the Eyring equation at 120 °C (393 K) to the data calculated using BP/TZP. [c]Assuming $\sigma_o = \sigma_p$. [d]From references [83,85,86]. [e]Parameters for di-substituted acids were calculated additively see ref [87] for precedent. [f]From the minimum perpendicular dimension of the NO_2 group.

Figure S1-1. Graphical representation and statistical significance of the Fujita-Nishioka model with experimental rates.



Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	0.9946	0.8099	1.228	0.25055	
Sigma	1.3718	0.5715	2.400	0.03988	*
Es	1.0530	0.2981	3.533	0.00639	**
F	5.2826	2.1811	2.422	0.03848	*

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.6843 on 9 degrees of freedom

Multiple R-squared: 0.7987, Adjusted R-squared: 0.7316

F-statistic: 11.91 on 3 and 9 DF, p-value: 0.00174

S1.2. – COMPUTATIONAL SECTION

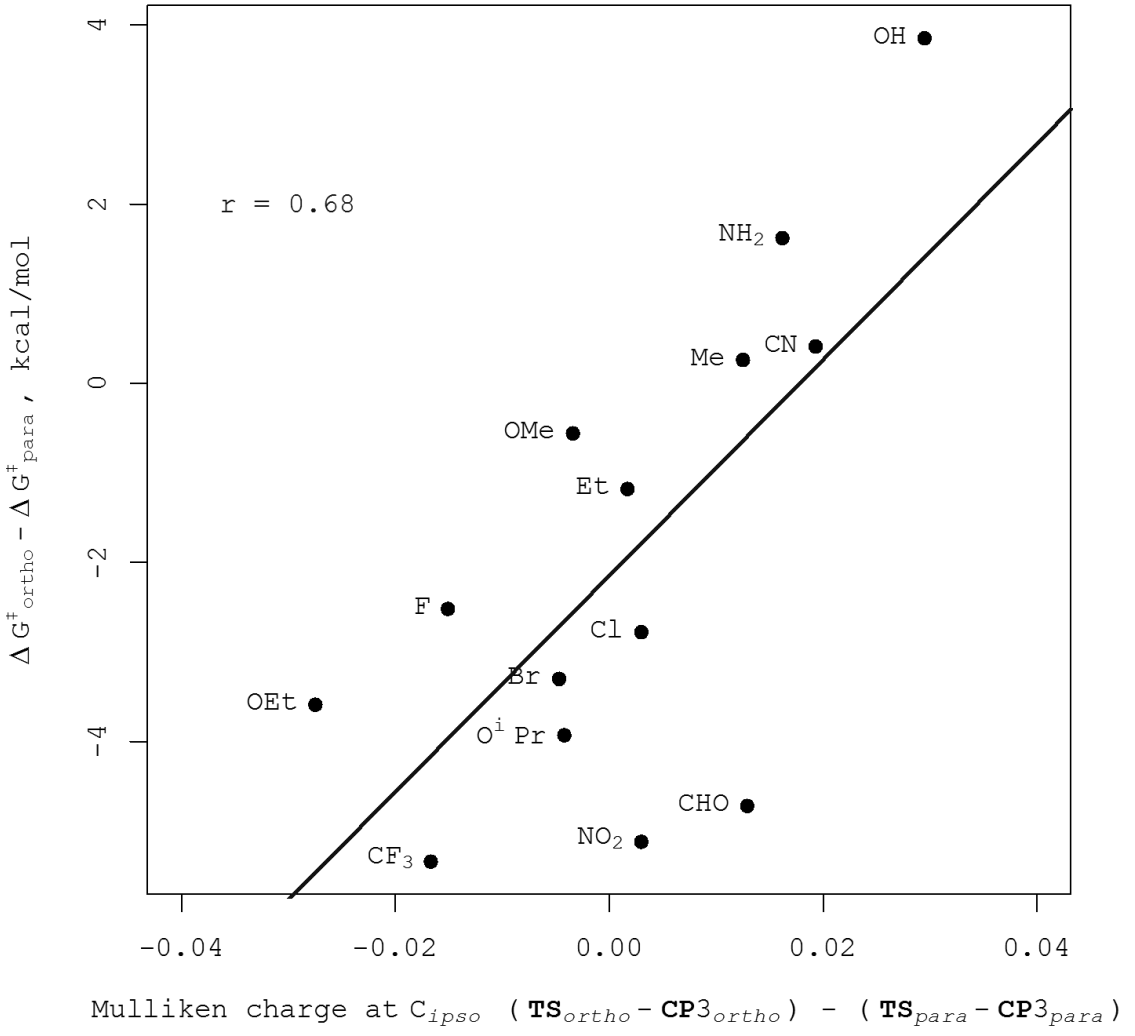
S1.2.1. – Activation energy for *ortho* compounds relative to *meta*

Table S1-2. Comparison of the relative free energy stability of **CP3** and **TS** structures for *ortho* and *meta* isomers of several substituted benzoic acids versus the relative activation barriers for decarboxylation at BP/TZP level of computation.

Entry	Substituent	$\Delta G^{\ddagger}_{ortho} - \Delta G^{\ddagger}_{meta}$ (kcal mol^{-1})	**CP3** $G_{ortho} - G_{meta}$ (kcal mol^{-1})	**TS** $G_{ortho} - G_{meta}$ (kcal mol^{-1})	$\Delta G^{\ddagger}_{ortho}$	Reactive Isomer
1	CF_3	-1.76	5.15	3.39	25.33	*Ortho*
2	NO_2	-4.94	4.60	-0.34	23.05	*Ortho*
3	CHO	-5.75	6.34	0.59	23.70	*Ortho*
4	O^{i}Pr	-2.68	5.14	2.46	24.55	*Ortho*
5	OEt	-3.57	3.57	0.00	25.00	*Ortho*
6	Br	-3.69	3.68	-0.01	24.11	*Ortho*
7	Cl	-1.62	2.11	0.49	25.33	*Ortho*
8	F	-4.01	4.01	0.00	24.39	*Ortho*
9	Et	-2.65	4.88	2.22	25.19	None
10	OMe	-1.21	0.98	-0.22	26.36	*Ortho*
11	Me	-0.43	3.12	2.68	25.48	None
12	CN	-0.50	1.09	0.60	27.38	None
13	NH_2	-0.86	-2.52	-3.38	26.50	None
14	OH	3.05	-6.65	-3.60	31.20	None

S1.2.2. – Correlation analysis

Figure S1-2. Correlation and its statistical significance between $\Delta G^{\ddagger}_{ortho}$-$\Delta G^{\ddagger}_{para}$ and Mulliken charge double difference at C_{ipso} between *TS* and *CP3* and also between *ortho* and *para*.



Pearson's product-moment correlation

t = 3.2058, df = 12, p-value = 0.00755

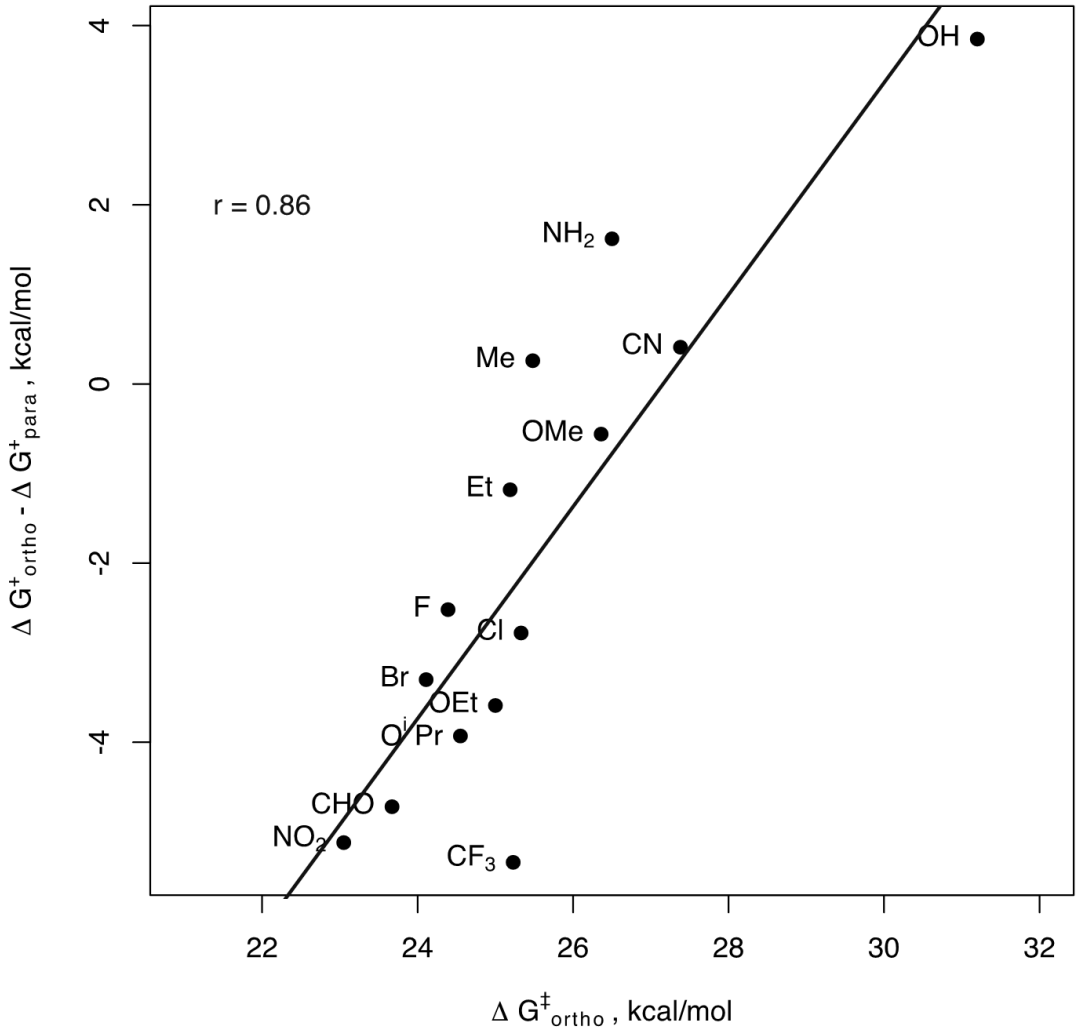
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.2323876 0.8893096

sample estimates: cor 0.6792193

Figure S1-3. Correlation and its statistical significance between $\Delta G^{\ddagger}_{ortho}$-$\Delta G^{\ddagger}_{para}$ and $\Delta G^{\ddagger}_{ortho}$ for the 14 substituents of Table 2.



Pearson's product-moment correlation

t = 5.8015, df = 12, p-value = 8.453e-05

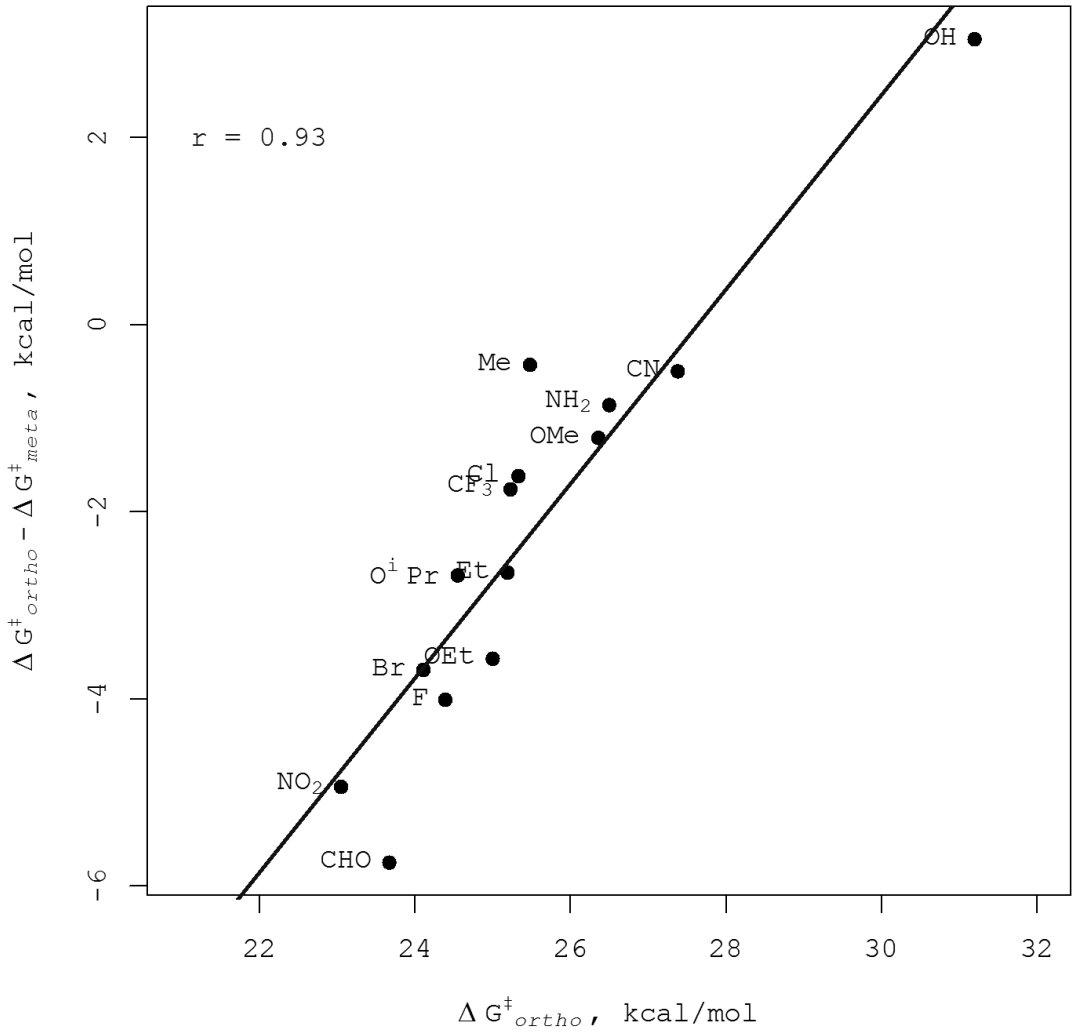
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.6024598 0.9543944

sample estimates: cor 0.8585889

Figure S1-4. Correlation and its statistical significance between $\Delta G^{\ddagger}_{ortho}$-$\Delta G^{\ddagger}_{meta}$ and $\Delta G^{\ddagger}_{ortho}$ for the 14 substituents of Table S1-2.



Pearson's product-moment correlation

t = 8.198, df = 11, p-value = 5.173e-06

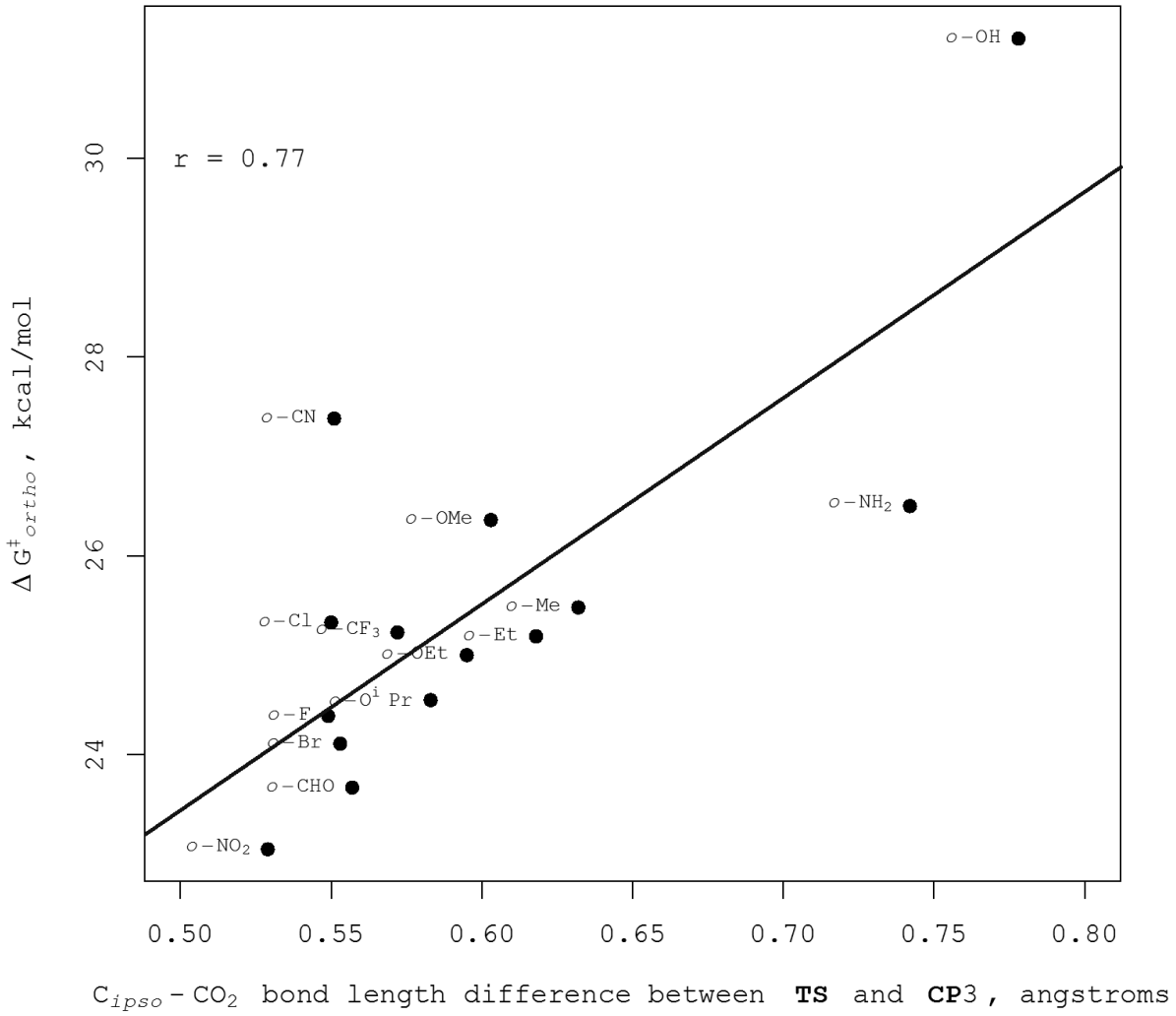
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.7686047 0.9783068

sample estimates: cor 0.9270104

Figure S1-5. Correlation and its statistical significance between C_{ipso}-CO_2 bond lengths and $\Delta G^{\ddagger}_{ortho}$ for *ortho* compounds only.



Pearson's product-moment correlation

t = 4.1583, df = 12, p-value = 0.001327

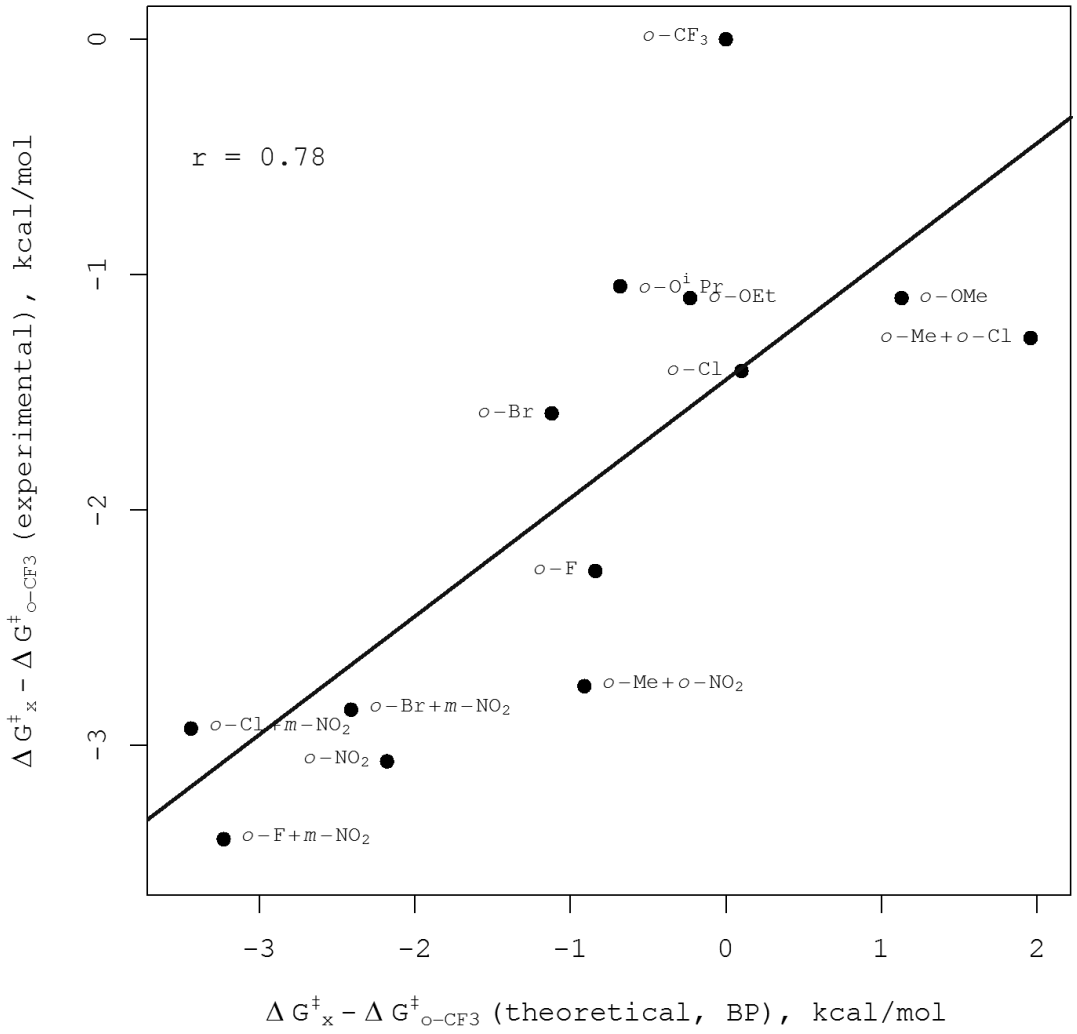
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.4013682 0.9227424

sample estimates: cor 0.7683266

Figure S1-6. Correlation plot and its statistical significance between BP and experimental relative activation energies.



Pearson's product-moment correlation

t = 4.083, df = 11, p-value = 0.001811

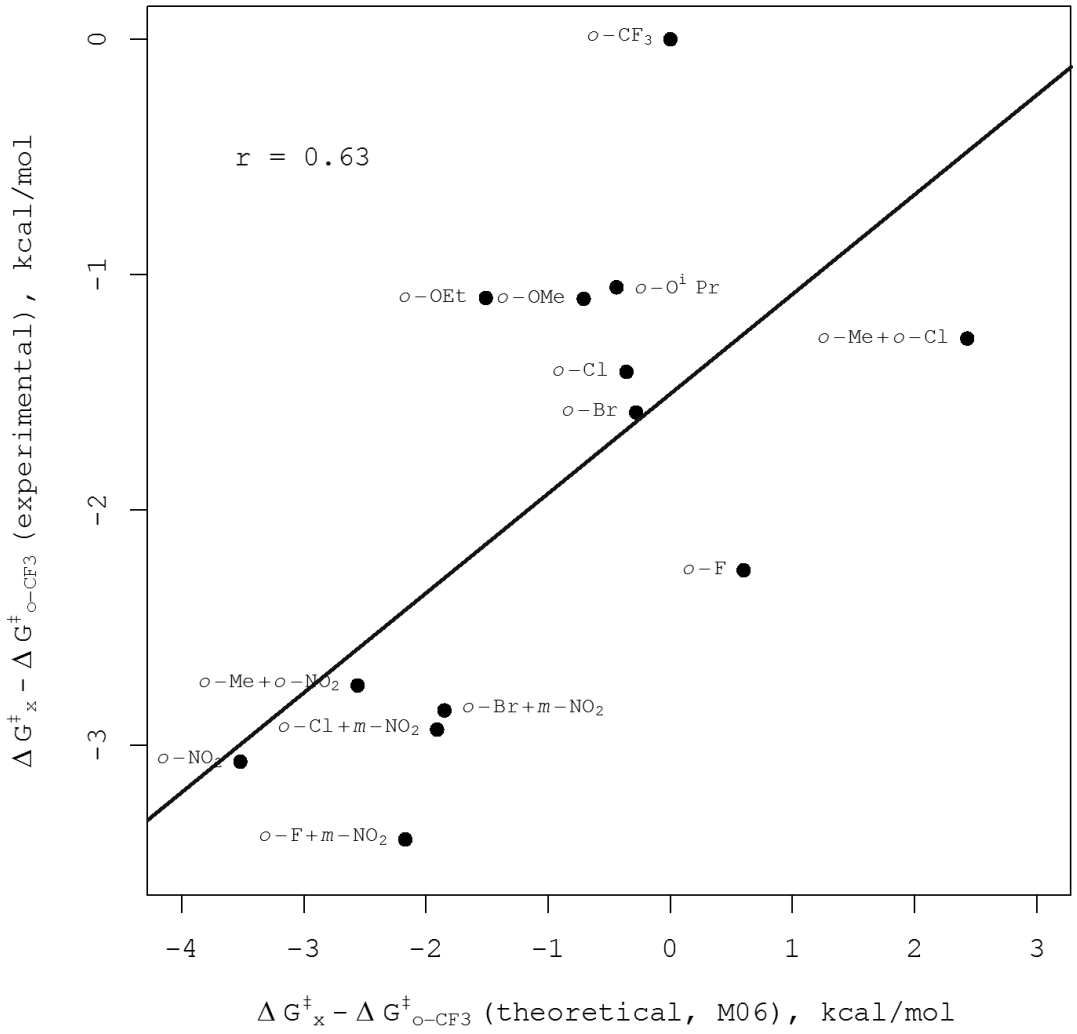
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.3934790 0.9296085

sample estimates: cor 0.7761862

Figure S1-7. Correlation plot and its statistical significance between M06 and experimental relative activation energies.



Pearson's product-moment correlation

t = 2.7141, df = 11, p-value = 0.02014

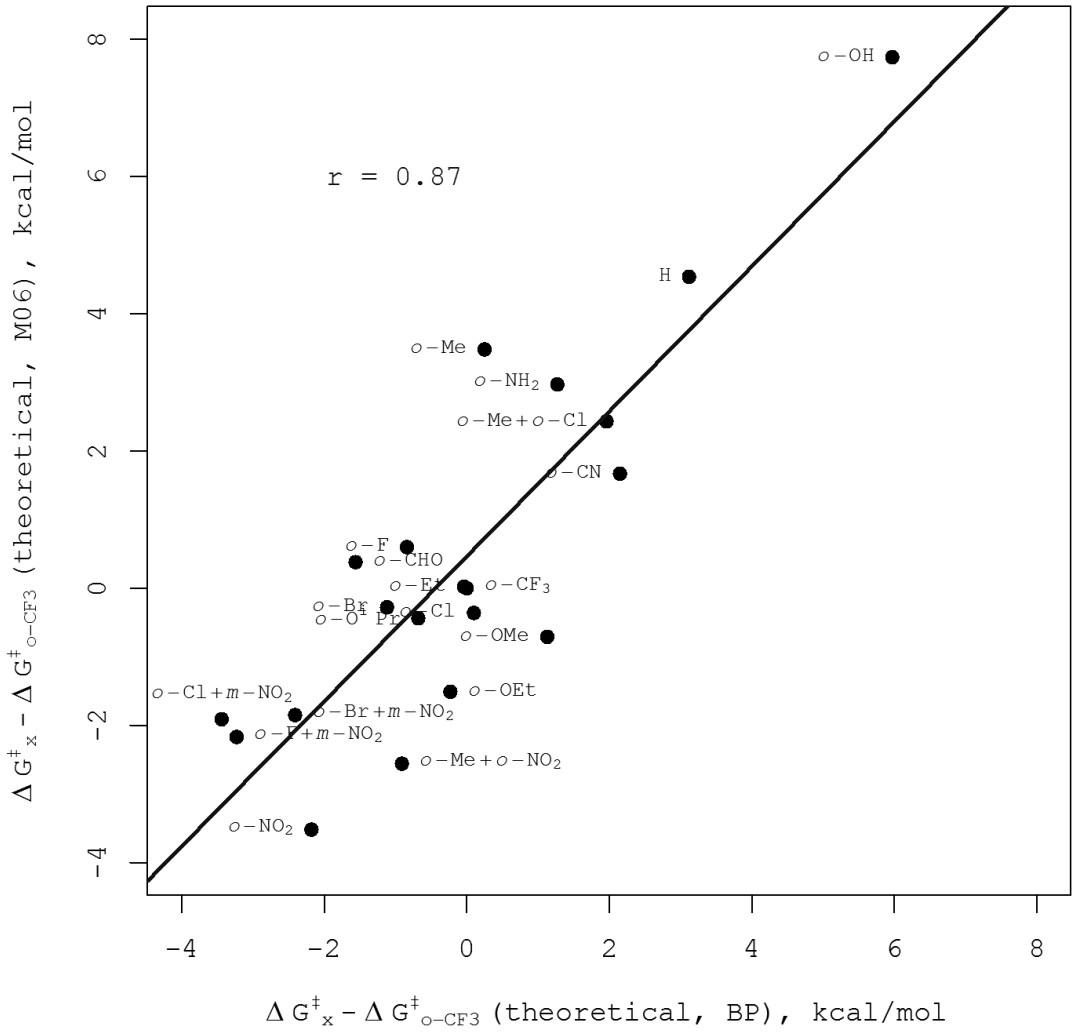
alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.1264368 0.8779396

sample estimates: cor 0.6333032

Figure S1-8. Correlation plot and its statistical significance between relative BP and M06 activation energies.



Pearson's product-moment correlation

t = 7.4497, df = 18, p-value = 6.659e-07

alternative hypothesis: true correlation is not equal to 0

95 percent confidence interval:

0.6928758 0.9472380

sample estimates: cor 0.8689624

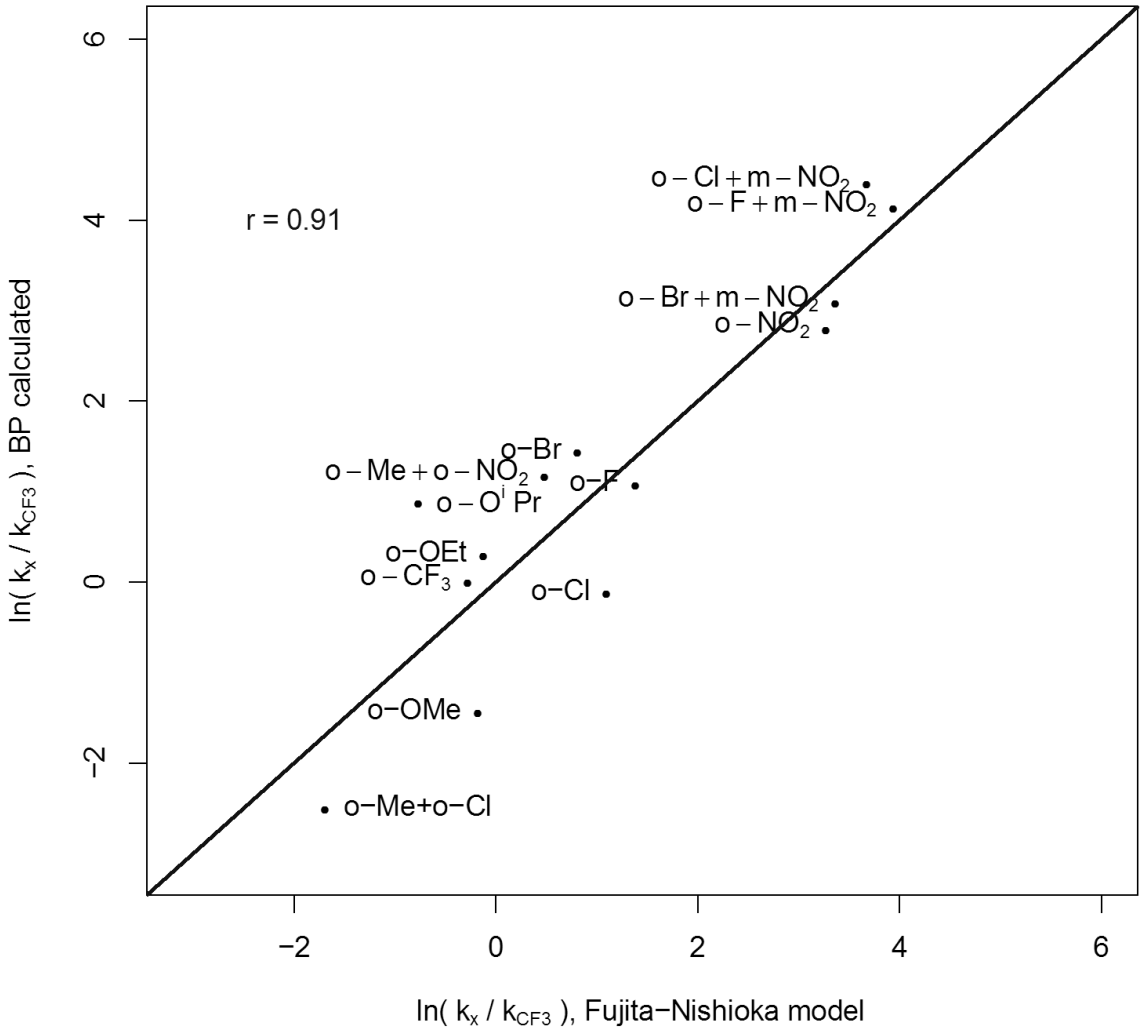
S1.2.3. – Regression analysis – LFER model

Table S1-3. Predefined parameters for all compounds used to build the Fujita-Nishioka model by multiple linear regression models.

Entry	Substituents[a]	$\ln \frac{k_x}{k_{CF_3}}$ BP[b]	$\ln \frac{k_x}{k_{CF_3}}$ M06[b]	$\sigma_{o,m,p}$ [c,d,e]	$-E_s^{c,o}$ [d,e]	F [d,e]
1	*o*-Cl+*m*-NO_2	4.40	2.45	0.94	-0.97	0.43
2	*o*-F+*m*-NO_2	4.13	2.78	0.77	-0.46	0.43
3	*o*-Br+*m*-NO_2	3.08	2.37	0.94	-1.16	0.44
4	*o*-NO_2	2.79	4.51	0.76	-1.01[f]	0.67
5	*o*-Br	1.43	0.36	0.23	-1.16	0.44
6	*o*-Me+*o*-NO_2	1.16	3.28	0.59	-2.25[f]	0.63
7	*o*-F	1.08	-0.77	0.06	-0.46	0.43
8	*o*-O^{i}Pr	0.87	0.56	-0.45	-0.55	0.30
9	*o*-OEt	0.29	1.93	-0.24	-0.55	0.22
10	*o*-CF_3	0.00	0.00	0.54	-2.40	0.38
11	*o*-Cl	-0.13	0.47	0.23	-0.97	0.41
12	*o*-OMe	-1.45	0.91	-0.27	-0.55	0.26
13	*o*-Cl+*o*-Me	-2.51	-3.11	0.06	-2.21	0.37

[a]The compounds are ranked according to the logarithmic experimentally calculated relative rate. [b]Derived by applying the Eyring equation at 120 °C (393 K) to the data calculated using BP/TZP. [c]Assuming $\sigma_o = \sigma_p$. [d]From references [83,85,86]. [e]Parameters for di-substituted acids were calculated additively see ref [87] for precedent. [f]From the minimum perpendicular dimension of the NO_2 group.

Figure S1-9. Plot of modified Fujita-Nishioka relationship against the BP theoretical logarithmic relative rates.



Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	1.4075	1.1536	1.220	0.25343	
Sigma	3.5928	0.8141	4.413	0.00169	**
Es	1.7139	0.4246	4.037	0.00294	**
F	1.3157	3.1067	0.424	0.68186	

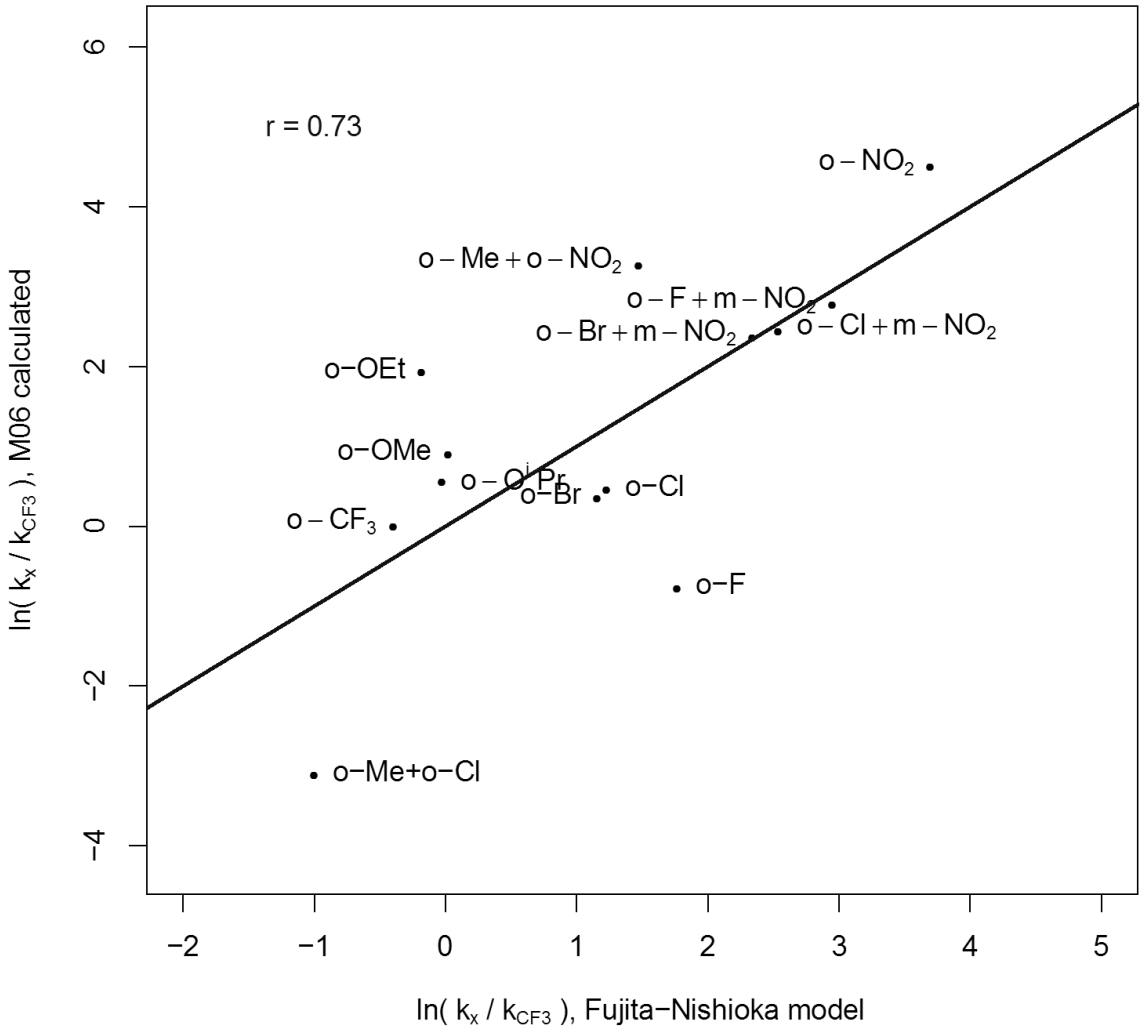
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.9747 on 9 degrees of freedom

Multiple R-squared: 0.8287, Adjusted R-squared: 0.7715

F-statistic: 14.51 on 3 and 9 DF, p-value: 0.0008556

Figure S1-10. Plot of modified Fujita-Nishioka relationship against the M06 theoretical logarithmic relative rates.



Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	-0.4089	1.8431	-0.222	0.829
Sigma	1.6655	1.3007	1.280	0.232
Es	1.3654	0.6783	2.013	0.075 .
F	6.3173	4.9636	1.273	0.235

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1.557 on 9 degrees of freedom

Multiple R-squared: 0.5338, Adjusted R-squared: 0.3784

F-statistic: 3.435 on 3 and 9 DF, p-value: 0.06551

S1.2.4. – Energies of stationary points

Table S1-4. Optimized energies (E_{opt}), Thermal enthalpies (H), Entropies (-TS) and free energy (G) of all computed compounds at the BP/TZP with ADF2009 (in kcal mol^{-1}).

Substituent	Compound	E_{opt}	H	-TS	G
CH_3COO-Ag/DMSO	CP2	-2164.06	-2077.67	-35.88	-2113.55
CO_2	CP5	-524.35	-517.08	-15.27	-532.36
CH_3COOH	CP7	-1067.46	-1028.80	-20.76	-1049.56
o-Cl	CP1	-2203.96	-2136.09	-28.03	-2164.12
o-Cl	CP3	-3302.14	-3187.22	-42.64	-3229.86
o-Cl	CP4	-2767.68	-2663.22	-36.33	-2699.56
o-Cl	CP6	-1686.17	-1628.76	-22.52	-1651.28
o -Cl	TS	-3276.42	-3163.22	-41.31	-3204.53
m-Cl	CP1	-2208.42	-2140.52	-27.86	-2168.38
m-Cl	CP3	-3305.75	-3190.79	-41.18	-3231.97
m-Cl	CP4	-2765.96	-2662.09	-34.68	-2696.77
m-Cl	TS	-3276.95	-3163.74	-41.28	-3205.02
p-Cl	CP1	-2208.88	-2140.96	-27.74	-2168.70
p-Cl	CP3	-3305.67	-3190.72	-42.10	-3232.82
p-Cl	CP4	-2765.18	-2660.61	-37.24	-2697.85
p-Cl	TS	-3276.99	-3163.75	-40.96	-3204.71
o-NO_2	CP3	-3689.55	-3566.20	-44.70	-3610.90
o-NO_2	TS	-3664.51	-3542.90	-44.95	-3587.85
m-NO_2	CP3	-3693.93	-3571.11	-44.39	-3615.50
m-NO_2	TS	-3664.45	-3542.80	-44.71	-3587.51
p-NO_2	CP3	-3693.52	-3570.74	-44.45	-3615.18
p-NO_2	TS	-3664.47	-3542.83	-44.18	-3587.01
o-F	CP3	-3346.46	-3230.94	-40.69	-3271.63
o-F	TS	-3321.53	-3208.31	-38.93	-3247.24
m-F	CP3	-3349.31	-3233.86	-41.78	-3275.64
m-F	TS	-3320.11	-3206.42	-40.82	-3247.24
p-F	CP3	-3349.53	-3234.64	-39.37	-3274.01
p-F	TS	-3320.36	-3206.61	-40.50	-3247.10
o-Br	CP3	-3287.21	-3172.52	-42.98	-3215.50
o-Br	TS	-3261.52	-3148.03	-43.44	-3191.47
m-Br	CP3	-3290.80	-3176.07	-43.11	-3219.18
m-Br	TS	-3262.06	-3149.12	-42.27	-3191.39
p-Br	CP3	-3291.40	-3176.66	-41.96	-3218.62
p-Br	TS	-3262.15	-3149.22	-42.06	-3191.29
o-OEt	CP3	-4234.71	-4074.79	-46.75	-4121.54
o-OEt	TS	-4208.77	-4051.15	-45.39	-4096.54
m-OEt	CP3	-4239.09	-4080.53	-44.58	-4125.11
m-OEt	TS	-4208.93	-4051.52	-45.02	-4096.53
p-OEt	CP3	-4240.10	-4080.86	-45.54	-4126.40

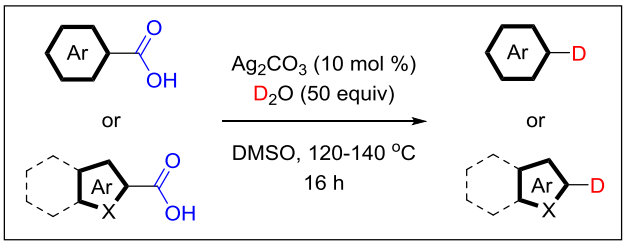
p-OEt	TS	-4209.71	-4052.22	-45.59	-4097.81
o-OMe	CP3	-3858.08	-3716.78	-43.90	-3760.68
o-OMe	TS	-3831.90	-3692.24	-42.08	-3734.31
m-OMe	CP3	-3861.63	-3720.91	-40.75	-3761.66
m-OMe	TS	-3831.94	-3693.03	-41.06	-3734.09
p-OMe	CP3	-3862.18	-3720.79	-43.44	-3764.23
p-OMe	TS	-3833.17	-3693.49	-43.85	-3737.34
o-O^{i}Pr	CP3	-4604.65	-4427.74	-46.59	-4474.33
o-O^{i}Pr	TS	-4579.62	-4404.91	-44.88	-4449.79
m-O^{i}Pr	CP3	-4610.46	-4434.24	-45.23	-4479.47
m-O^{i}Pr	TS	-4579.52	-4403.78	-48.46	-4452.25
p-O^{i}Pr	CP3	-4611.57	-4434.06	-48.40	-4482.46
p-O^{i}Pr	TS	-4581.74	-4406.55	-47.43	-4453.98
o-CHO	CP3	-3690.60	-3563.71	-42.53	-3606.23
o-CHO	TS	-3665.07	-3539.34	-43.22	-3582.57
m-CHO	CP3	-3695.21	-3567.77	-44.80	-3612.57
m-CHO	TS	-3665.98	-3540.87	-42.29	-3583.15
p-CHO	CP3	-3694.62	-3567.76	-42.77	-3610.53
p-CHO	TS	-3665.46	-3541.01	-41.13	-3582.14
o-CF_3	CP3	-3740.54	-3616.51	-43.76	-3660.27
o-CF_3	TS	-3713.43	-3590.50	-44.54	-3635.04
m-CF_3	CP3	-3745.97	-3621.88	-43.54	-3665.42
m-CF_3	TS	-3716.80	-3594.49	-43.93	-3638.42
p-CF_3	CP3	-3745.91	-3621.27	-45.93	-3667.20
p-CF_3	TS	-3716.73	-3594.37	-42.26	-3636.63
o-CN	CP3	-3634.69	-3514.41	-42.67	-3557.08
o-CN	TS	-3606.41	-3487.89	-41.81	-3529.70
m-CN	CP3	-3636.57	-3516.26	-41.91	-3558.17
m-CN	TS	-3607.13	-3489.19	-41.10	-3530.29
p-CN	CP3	-3636.28	-3516.61	-40.55	-3557.16
p-CN	TS	-3606.78	-3488.23	-41.96	-3530.19
o-Me	CP3	-3717.51	-3579.65	-40.88	-3620.53
o-Me	TS	-3690.05	-3554.00	-41.05	-3595.05
m-Me	CP3	-3721.38	-3584.09	-39.56	-3623.65
m-Me	TS	-3691.40	-3555.40	-42.34	-3597.73
p-Me	CP3	-3721.33	-3584.05	-39.82	-3623.87
p-Me	TS	-3691.83	-3555.81	-42.84	-3598.65
o-Et	CP3	-4089.97	-3933.35	-44.32	-3977.67
o-Et	TS	-4063.08	-3908.84	-43.65	-3952.49
m-Et	CP3	-4094.12	-3938.13	-44.42	-3982.55
m-Et	TS	-4063.85	-3909.71	-45.00	-3954.71
p-Et	CP3	-4094.52	-3939.09	-41.84	-3980.93
p-Et	TS	-4065.08	-3910.84	-43.72	-3954.56
o-OH	CP3	-3505.58	-3382.12	-41.72	-3423.84
o-OH	TS	-3472.37	-3350.26	-42.38	-3392.64
m-OH	CP3	-3498.31	-3375.11	-42.08	-3417.19

m-OH	TS	-3469.12	-3347.68	-41.37	-3389.04
p-OH	CP3	-3499.33	-3376.66	-39.94	-3416.61
p-OH	TS	-3470.11	-3348.56	-40.70	-3389.26
o-NH_2	CP3	-3623.84	-3492.91	-41.51	-3534.42
o-NH_2	TS	-3594.97	-3465.01	-42.91	-3507.92
m-NH_2	CP3	-3622.48	-3491.40	-40.50	-3531.91
m-NH_2	TS	-3592.61	-3463.38	-41.17	-3504.55
p-NH_2	CP3	-3624.06	-3492.97	-40.55	-3533.52
p-NH_2	TS	-3594.92	-3465.00	-43.63	-3508.64
H	CP3	-3344.16	-3218.82	-39.12	-3257.95
H	TS	-3314.46	-3190.88	-38.72	-3229.60
o-F+*m*-NO_2	CP3	-3695.63	-3577.39	-44.82	-3622.22
o-F+*m*-NO_2	TS	-3671.13	-3554.59	-45.62	-3600.21
o-Cl+*m*-NO_2	CP3	-3651.58	-3534.57	-43.08	-3577.65
o-Cl+*m*-NO_2	TS	-3625.99	-3510.10	-45.77	-3555.87
o-Br+*m*-NO_2	CP3	-3636.23	-3518.87	-46.51	-3565.38
o-Br+*m*-NO_2	TS	-3612.55	-3496.87	-45.70	-3542.57
o-NO_2+*o*-Me	CP3	-4066.18	-3925.41	-47.44	-3972.84
o-NO_2+*o*-Me	TS	-4038.83	-3900.13	-46.71	-3946.84
o-Cl+*o*-Me	CP3	-3679.18	-3545.93	-45.33	-3591.26
o-Cl+*o*-Me	TS	-3650.40	-3518.87	-45.20	-3564.07

Table S1-5. Optimized energies (E_{opt}), Thermal enthalpies (H), Entropies (-TS) and free energy (G) of all computed compounds at the M06/6-31G(d) functional with Gaussian09 (in kcal mol^{-1}).

Substituent	Compound	E_{opt}	H	-TS	G
o-Br	CP3	-2315190.55	-2315069.28	-43.97	-2315113.25
o-Br	TS	-2315012.65	-2315046.64	-42.77	-2315089.41
o-CF_3	CP3	-913514.02	-913381.95	-46.60	-913428.54
o-CF_3	TS	-913318.04	-913360.46	-43.96	-913404.42
o-CH_3	CP3	-726734.91	-726589.81	-43.46	-726633.27
o-CH_3	TS	-726503.08	-726564.91	-40.75	-726605.66
o-Me+*o*-Cl	CP3	-1015117.87	-1014978.25	-45.40	-1015023.65
o-Me+*o*-Cl	TS	-1014901.77	-1014954.27	-42.83	-1014997.10
o-Me+*o*-NO_2	CP3	-855005.74	-854857.27	-46.61	-854903.88
o-Me+*o*-NO_2	TS	-854779.90	-854837.98	-44.35	-854882.32
o-CN	CP3	-759934.98	-759807.94	-43.35	-759851.29
o-CN	TS	-759741.07	-759784.42	-41.08	-759825.50
o-CHO	CP3	-773162.23	-773028.30	-43.38	-773071.68
o-CHO	TS	-772956.04	-773006.02	-41.16	-773047.18
o-Cl	CP3	-990465.37	-990343.88	-43.10	-990386.98
o-Cl	TS	-990283.78	-990322.80	-40.43	-990363.22
o-Et	CP3	-751382.11	-751218.08	-43.99	-751262.06
o-Et	TS	-751119.31	-751194.44	-43.48	-751237.93
o-F	CP3	-764338.98	-764216.82	-43.87	-764260.69
o-F	TS	-764155.34	-764196.07	-39.90	-764235.97
o-NH_2	CP3	-736807.24	-736669.02	-41.96	-736710.97
o-NH_2	TS	-736587.94	-736643.10	-40.78	-736683.88
o-NO_2	CP3	-830353.38	-830223.35	-44.81	-830268.16
o-NO_2	TS	-830161.18	-830205.44	-42.11	-830247.56
o-OMe	CP3	-773907.37	-773758.28	-44.74	-773803.02
o-OMe	TS	-773674.60	-773737.26	-42.34	-773779.61
o-OEt	CP3	-798559.46	-798391.86	-46.02	-798437.88
o-OEt	TS	-798293.68	-798371.00	-44.28	-798415.27
o-OH	CP3	-749280.18	-749149.92	-42.46	-749192.39
o-OH	TS	-749071.68	-749120.58	-39.94	-749160.52
o-O^{i}Pr	CP3	-823206.49	-823020.81	-49.49	-823070.30
o-O^{i}Pr	TS	-822908.39	-823000.90	-45.72	-823046.62
H	CP3	-702086.03	-701959.10	-40.47	-701999.57
H	TS	-701885.27	-701931.42	-39.49	-701970.91
o-Br+*m*-NO_2	CP3	-2443461.72	-2443336.93	-47.50	-2443384.43
o-Br+*m*-NO_2	TS	-2443285.06	-2443316.16	-46.00	-2443362.16
o-Cl+*m*-NO_2	CP3	-1118737.24	-1118612.27	-46.87	-1118659.14
o-Cl+*m*-NO_2	TS	-1118558.29	-1118592.28	-44.65	-1118636.93
o-F+*m*-NO_2	CP3	-892611.91	-892486.32	-46.60	-892532.92
o-F+*m*-NO_2	TS	-892431.76	-892466.09	-44.88	-892510.97

Chapter 2 – Selective Deuteration of Aromatic Compounds via Deuterodecarboxylation of (Hetero)aromatic Carboxylic Acids



2.1 INTRODUCTION

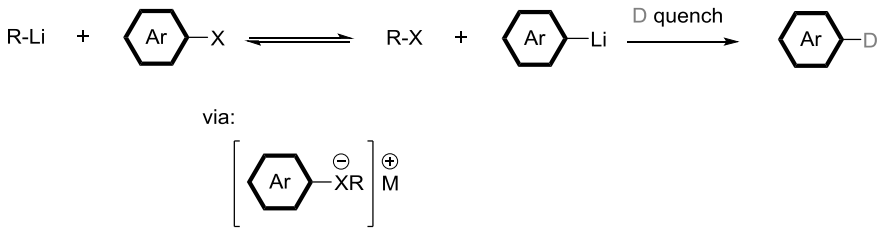
Synthetic procedures which successfully incorporate deuterium (D) and tritium (T) into organic molecules are highly sought after for a plethora of applications:[90] deuterium-labelled compounds are commonly used for mechanistic investigations of catalytic cycles and reaction pathways,[91] in stable-isotope tracer studies and as analytical standards,[92] neutron scattering,[93] and for the synthesis of drug compounds with enhanced metabolic stability.[94] On the other hand, tritium is arguably the most versatile radionuclide available, with tritiated compounds regularly exploited as radiotracers in the pharmaceutical industry from drug discovery level to clinical studies.[90,95] Synthetic methods for the preparation of deuterated compounds are regularly applied towards the synthesis of their tritium-labelled isotopologues, providing a corresponding tritium source can be accessed. Moreover, deuteration methodologies are commonly used as synthesis optimisation tools for subsequent tritium labelling.[90]

2.2. CURRENT METHODOLOGIES FOR DEUTERIUM INCORPORATION

Despite the high demand, methods for the selective incorporation of a single deuterium into an aromatic ring are scarce.[90,96,97] The most common protocol involves halogen/D exchange; this is usually mediated by strong bases, however, a consequent limitation in functional group scope is inherent. H/D exchange reactions can also be employed with the use of strong acids,[98] bases,[99] or transition metal catalysts.[100] Nonetheless, these processes are generally non-selective, and a limited number of examples are known where good selectivity is achieved.[101] Accordingly, there is a great need for the development of mild and selective methodologies for the incorporation of deuterium into aromatic rings.

2.2.1. Halogen/D exchange

Chemical methods which achieve hydro-dehalogenation of organic halides are readily used for deuterium incorporation, providing a suitable deuterium source is available. Common routes include catalytic hydrogenation, reduction with metals or low valent organometallic compounds, reduction with metal hydrides or reduction with strongly nucleophilic neutral or anionic species.[96] A wide variety of dehalogenation methods are available due to the unwanted impact that halogenated compounds have on the environment. However, from a synthetic standpoint, organohalides are favoured for C–D bond formation via metal-halogen exchange as this method offers high selectivity, with deuteration occurring exclusively on the carbon atom previously bonded to the halogen and generally affording excellent levels of deuterium incorporation. A number of methods have been reported using reducing metals in their elemental state, including but not limited to: Li, Na, Mg, In etc.[96,102] However, solutions of organolithium in hydrocarbon solvents are most commonly used to effect deutero-dehalogenation as they are inexpensive, relatively easy to handle and have wide commercial availability. The rate of carbon-halogen bond cleavage is well understood following the trend I>Br>Cl>>F and are directly related to the bond dissociation energies (BDE).[iv] On the other hand, the mechanism of lithium-halogen metathesis is still debated with both single electron transfer (S.E.T) and ionic pathways proposed; the nature of the mechanism is largely dependent on the halogen and the hybridisation of its bonded carbon atom. For aryl halides, it is widely accepted that the reaction proceeds via an anionic pathway in which the organometallic species undergoes nucleophilic attack onto the halide to form an 'ate' complex which then disproportionates to form a new organolithium and organohalide.[104] Deuteration occurs at the end of the reaction on addition of D_2O or acid which quenches any reactive organometallic species forming the C–D bond in turn (Scheme 48).



Scheme 48. General scheme illustrating halogen-deuterium exchange via metallation.

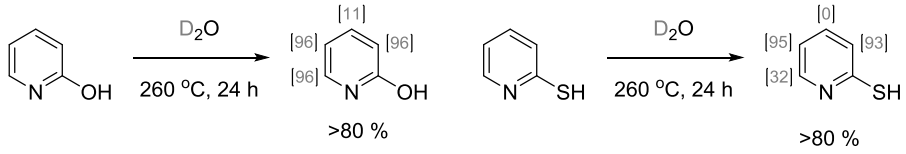
The main limitations of this approach are predicated by the basic and nucleophilic nature of the reagents required and organometallic species generated in the process. These limitations include handling issues, poor functional group tolerance and competing deprotonation of moderately acidic

[iv] Ph–X BDE; (C–I = 67.0 kcal mol^{-1}, C–Br = 84.0 kcal mol^{-1}, C–Cl = 97.1 kcal mol^{-1}, C–F = 127.2 kcal mol^{-1}).[103]

sites. Moreover, there is the requirement for stoichiometric amounts of metals as the deuterium source can only be introduced at the end of the reaction after halogen-metal exchange has occurred.

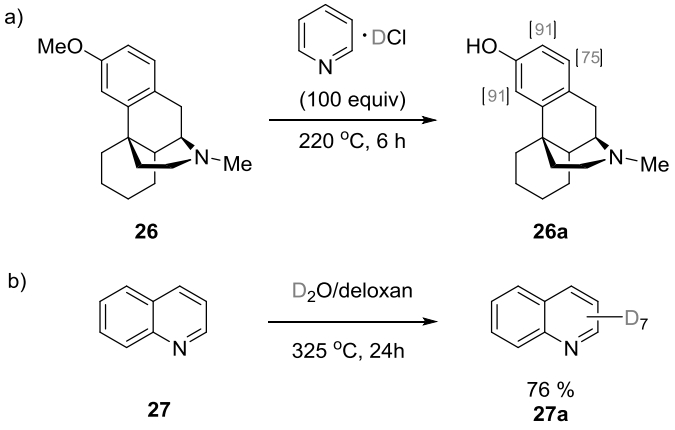
2.2.2. H/D exchange pH dependent – Acid catalysed

Deuterium incorporation in aromatic systems can occur by heating to elevated temperatures in deuterated solvents (Scheme 49),[105] exchange occurs via electrophilic aromatic substitution. Apart from the temperature the other main limitations result from the nature of the reaction, with regioselectivity being substrate dependent, this can result in excellent levels of deuteration in activated positions on the arene, poor or no deuteration in unactivated positions and poor regioselectivity. Increasingly microwave irradiation has been used to shorten reaction times affording comparable or improved levels of deuterium incorporation.[106]

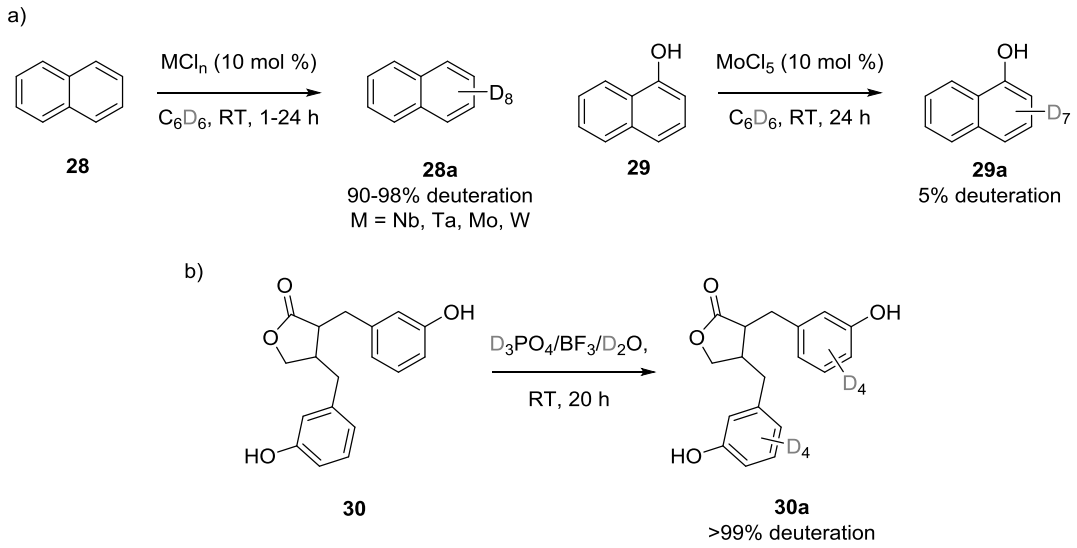


Scheme 49. H/D exchange of pyridine derivatives in D_2O at elevated temperatures.[105]

Improved arene H/D exchange can be offered with the use of Brønsted or Lewis acids in the presence of a deuterium source. A number of groups have utilised both deuterated and non-deuterated Brønsted acid catalysis to obtain high levels of deuteration (Scheme 50). Mürdter *et al.* showed that when heated in an excess of pyridinium deuterochloride, dextromethorphan (**26**) undergoes concomitant deuteration and *O*-demethylation to yield **26a**.[107] In this case, the harsh conditions gave fortuitous formation of the tri-deutero active metabolite dextrophan **26a**; nonetheless the forcing conditions required to achieve good levels of deuteration with Brønsted acid catalysis can be a limitation.



Scheme 50. Examples of Brønsted acid catalysed H/D exchange; a) deuterated acids e.g. pyridinium deuterochloride or b) non-deuterated acids such as Deloxan the polymer bound sulfonic acid can be used when combined with a deuterium source.[107,108]

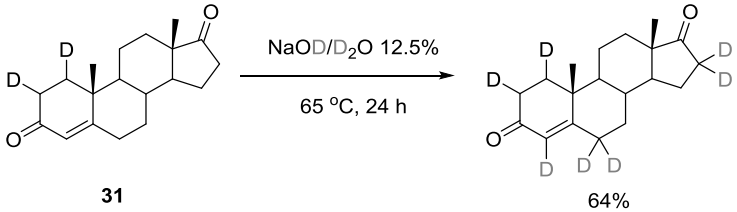


Scheme 51. Examples of Lewis acid catalysed H/D exchange; a) excellent levels of deuteration can be obtained at low temperatures, only in the absence of nucleophilic functional groups;[110] b) the addition of deuterated Brønsted acids help to overcome functional group intolerance.[111]

The rate of H/D exchange with Brønsted acids has been improved by employing microwave irradiation;[109] however the addition of a Lewis acid is necessary to achieve deuteration at lower temperatures. Group 3 (B, Al) and early transition metals (Nb, Ta, Mo, W) halides have been shown to facilitate deuteration at room temperature with C_6D_6 (Scheme 51). This approach is limited to unactivated arenes (e.g. **28**) with poor yields observed in the presence of nucleophilic functional groups (**29**), presumably due to an unwanted interaction with the Lewis acid (Scheme 51a).[110] When these Lewis acids are used in combination with deuterated Brønsted acids, an improved functional group tolerance was shown by Wähälä and co-workers, allowing for the perdeuteration of polyphenols (**30**).[98b,111]

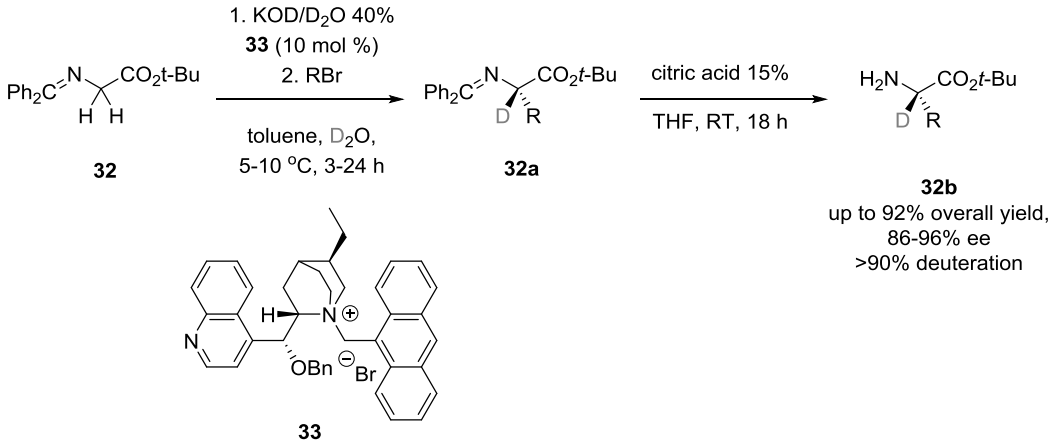
2.2.3. H/D exchange pH dependent – Base catalysed

Base catalysed routes to deuterium incorporation offer improved selectivity over acid catalysed processes. The increased acidity of sites adjacent to activated heteroatoms or compounds with enolisable hydrogens are frequently exploited for selective H/D exchange (Scheme 52).[112] The nature of these approaches means that they are usually carried out at low temperatures permitting for excellent stereocontrol.



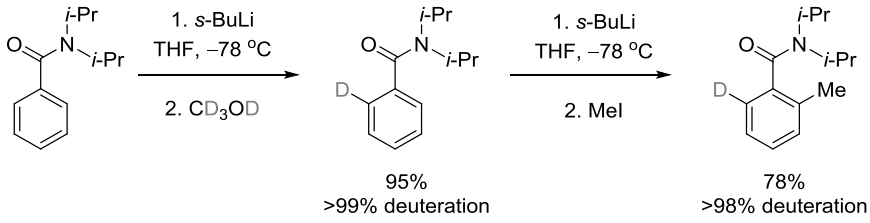
Scheme 52. Aqueous base catalysed H/D exchange of the enolisable protons in androstenedione **31**[112]

Accordingly, Lygo and co-workers reported the stereoselective synthesis of α-deuterated amino acids from benzophenone-derived glycine imine **32** using a chiral phase transfer catalyst **33**.[113] The mild and selective deuteration, alkylation and subsequent imine hydrolysis allows access to a variety of *t*-butyl amino acid esters (**32b**) with excellent yields and ee (Scheme 53). The only comparable acid catalysed route to deuterated amino acids requires separation of the racemate by preparative HPLC on chiral stationary phase.[114]



Scheme 53. Stereoselective synthesis of α-deuterated amino acids reported by Lygo *et al.*[113]

As previously discussed, organometallic species formed from metal/halogen exchange can undergo deuterolysis; this approach can also be applied using stoichiometric amounts of strong bases (usually organolithiums). Deprotonation irreversibly forms a lithiated intermediate which can be deuterodemetallated using D_2O, MeOD, AcOD, etc.[115] In aromatic systems selective deuteration can be achieved using a variety of different functional groups. via directed lithiation and subsequent deuteration *ortho* to the chelating group.[116] Moreover, Clayden and co-workers have shown that the incorporation of a deuterium in *ortho* offers a significantly large kinetic isotope effect (KIE), allowing the deuterium atom to act as a protecting group for the carbon, preventing further functionalisation at the site (Scheme 54).[116c]

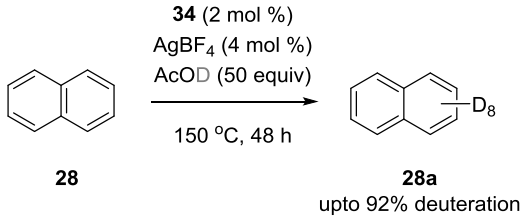


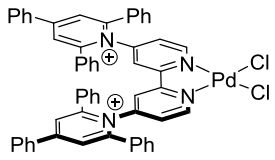
Scheme 54. *ortho*-deuteration via directed-metallation deprotonation, then deuterium quench. The new C-D bond offers a large KIE preventing subsequent deprotonation.[116c]

2.2.4. H/D exchange – Transition metal catalysed

Homogenous transition metal catalysed H/D exchange processes offer a number of advantages over other routes. Namely the reaction conditions are much milder with greater functional group tolerance; as a result, classical problems encountered with acid and base catalysed methodologies such as protecting group degradation and side chain deprotonation are avoided.[90]

Since the influential studies of Garnett, Shilov and co-workers to probe the functionalisation of inert C–H bonds, many efficient methods have been developed to utilise mid to late transition metal complexes to exchange H/D bonds.[117] In arenes, this can either involve extensive conversion at all aromatic carbons using Ru, Rh, Ir, Pd, or Pt complexes[90,118] or alternatively selective *ortho*-deuteration can be achieved using a chelating group to direct the metallation of Ir, Pd or Pt complexes.[119]





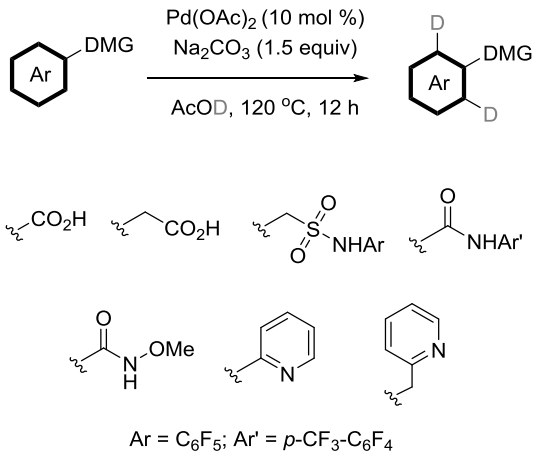
34

Scheme 55. Per-deuteration reported by Sanford *et al.* using a variety of Pd and Pt catalysts.[118]

There is an abundance of perdeuteration methodologies in the literature using a variety of transition metal complexes. Recently, Sanford and co-workers reported the Pd and Pt catalysed H/D exchange of arenes in the presence of a number of different deuterium sources (Scheme 55).[118] Their presented work gives an extensive study of the rate and efficiency of a number of different complexes on the C–H activation of arenes, using H/D exchange as an analytical marker. Their presented work is particularly interesting as a mechanistic study on C–H activation but due to the high cost of the metals and ligands used, it is not really a viable deuteration methodology.

In 2013, Yu and co-workers reported a directed Pd catalysed deuteration methodology in which they demonstrate the *ortho*-deuteration of a variety of different arenes using deuterated acetic acid as the solvent (Scheme 56).[119d] The reaction exhibits good functional group tolerance (CF_3, NO_2, OMe etc) and works in the presence of halogens which are largely resistant to oxidative addition with Pd (F, Cl), thus there are no examples containing Br or I. This methodology exhibits good selectivity for

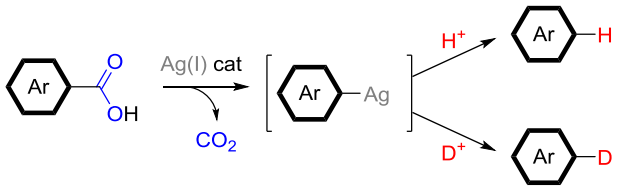
monodeuteration providing the *ortho*-position is blocked otherwise di-*ortho* deuteration occurs. Superfluous deuteration is also observed in the carboxylic acid and sulfonamide side chains which contain acidic α-protons. For these directing groups an additional reprotonation step is required where the deuterated product is heated to 120 ^{o}C in excess NaOH for a further 12 hours.



Scheme 56. The Pd catalysed *ortho*-deuteration reported by Yu *et al.* is compatible with a number of different directing groups.[119d]

2.3. AIMS OF THE PROJECT

Previous work in the group has shown that *ortho*-substituted benzoic and heteroaromatic α-carboxylic acids can be protodecarboxylated in the presence of sub-stoichiometric amounts of Ag_2CO_3.[25] The reaction is thought to proceed via an aryl-Ag(I) intermediate that is subsequently protonated. We hypothesised that if this reaction was carried out in the presence of a D^+ source, selective deuterium incorporation could occur (Scheme 57).[120]



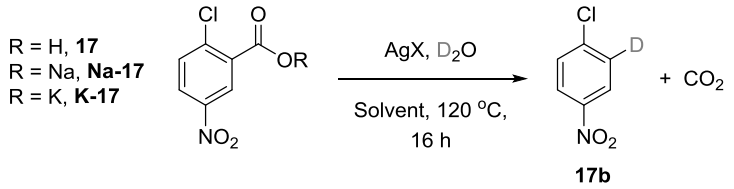
Scheme 57. The Ag(I)-catalysed proto- and deutero-decarboxylation of benzoic acids.

Preliminary results showed that the protodecarboxylation conditions could be adapted with the addition of deuterated solvents (D_2O, MeOD, EtOD) to facilitate deutero-decarboxylation in moderate to good yields.[121] This was extremely promising as a Ag-catalysed decarboxylative deuteration methodology would provide a selective, economical alternative to traditional protocols.

2.4. OPTIMISATION

In order to completely avoid the presence of H^+ in the reaction, the decarboxylation was initially tested with Na and K salts of 2-chloro-5-nitrobenzoic acid (**17**), a variety of Ag(I) salts which could undergo anion exchange and 10 equiv of D_2O (Table 6, entries 1-10). Overall, relatively good levels of deuterium incorporation were observed in the resulting arene **17a**, however the yields were variable. The best result of 67% yield/91% deuteration was obtained using the Na-carboxylate (**Na-17**), AgOAc and DMA as the solvent (Table 6, entry 6). However, in the analogous protodecarboxylation reaction, the commercially available acid **17** undergoes quantitative conversion in a benign reaction solvent (DMSO) (Table 6, entry 11). When this is taken into account, it is obvious that a new approach is needed as the current one is comparatively low yielding, requires the preformation of the carboxylate and uses a toxic solvent.

Table 6. Optimisation of the deuterodecarboxylation[a]



17b

Entry	Substrate	AgX (mol%)	D_2O (equiv)	Solvent	Yield (%)[b]	D (%)[c]
1	**Na-17**	AgOTFA (20)	10	DMSO	20	92
2	**Na-17**	$AgBF_4$ (20)	10	DMSO	26	82
3	**Na-17**	$AgNO_3$ (20)	10	DMSO	35	87
4	**Na-17**	AgOAc (20)	10	DMSO	11	86
5	**Na-17**	AgOAc (20)	10	DMF	61	85
6	**Na-17**	AgOAc (20)	10	DMA	67	91
7	**K-17**	AgOTFA (20)	10	DMF	30	70
8	**K-17**	$AgBF_4$ (20)	10	DMF	38	80
9	**K-17**	$AgNO_3$ (20)	10	DMF	39	77
10	**K-17**	AgOAc (20)	10	DMF	20	77
11	**17**	Ag_2CO_3 (10)	0	DMSO	>99	0
12	**17**	Ag_2CO_3 (10)	10	DMSO	>99	71
13	**17**	Ag_2CO_3 (10)	20	DMSO	94	77
14	**17**	Ag_2CO_3 (10)	30	DMSO	92	79
15	**17**	Ag_2CO_3 (10)	40	DMSO	95	86
16	**17**	Ag_2CO_3 (10)	50	DMSO	92	92
17	**17**	Ag_2CO_3 (10)	100	DMSO	48	91

[a]Reaction conditions: all reactions were carried out under a N_2 atmosphere with 1.0 equiv of substrate and the stated amounts of AgX and D_2O in 0.5 mL of solvent, at 120 °C for 16 h. [b]The yield of **5b** was determined by ^1H NMR analysis using mesitylene as an internal standard. [c]The extent of deuteration of **5b** was determined by ^1H NMR analysis using mesitylene as an internal standard.

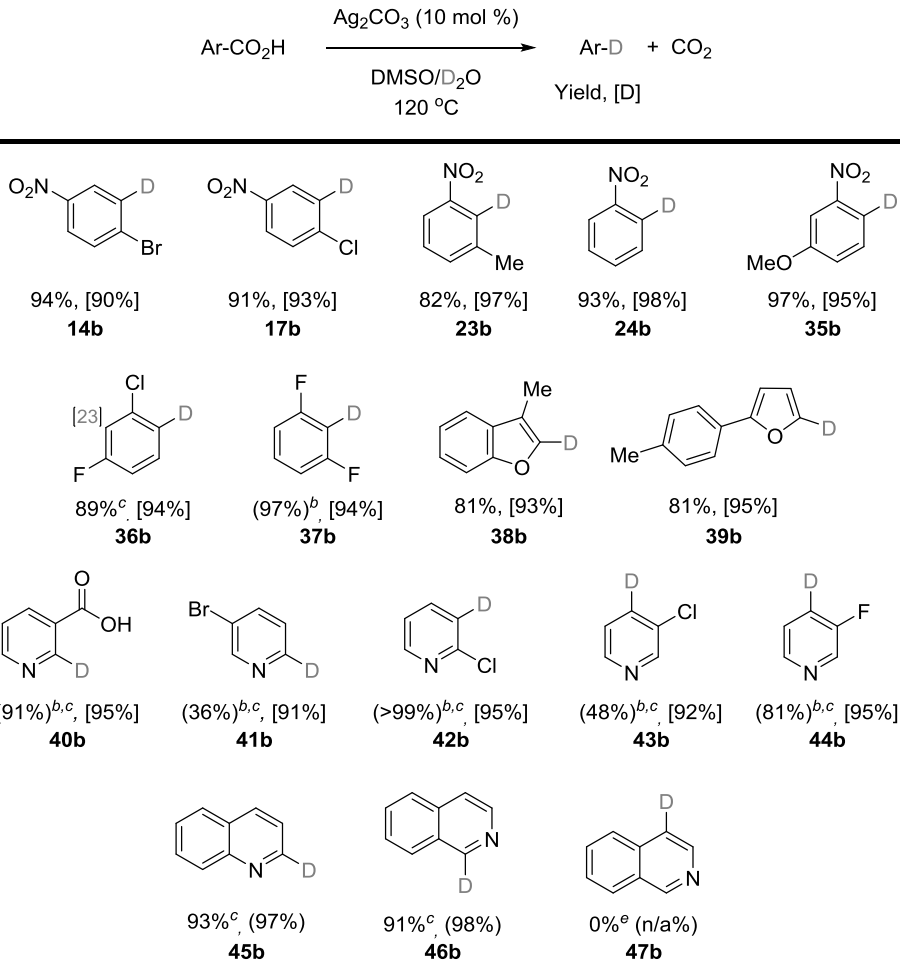
The direct decarboxylation from carboxylic acid **17** was explored with Ag_2CO_3 and varying amounts of D_2O (Table 6, entries 11-17). On increasing the amount of D_2O from 0 to 50 equiv, consistently high conversion was observed and deuteration increased to a maximum of 92% (Table 6, entries 11-16). This was found to be the optimal amount, as conversion dropped significantly when 100 equiv of D_2O were used. It was surprising that the use of a large excess of D_2O did increase the extent of deuterium incorporation (Table 6, entries 17).

2.5. SUBSTRATE SCOPE

With the optimised protocol in hand, the scope of the reaction was examined (Table 7). The standard reaction conditions consistently afforded high levels of deuterium incorporation (91-99%) good to high product yields (with 14 examples >81%). Several substituted benzoic and heteroaromatic acids were successfully reacted, with a variety of synthetically useful substituents reported, such as nitro (**14b**, **17b**, **23-24b**, **35b**), bromo (**14b**, **41b**), chloro (**17b**, **36b, 42-43b**) and fluoro (**36-37b**, **32b**). The regioselectivity of the decarboxylation allows for selective deuteration of

furans at position 2 (**38**-**39b**) and selective deuteration of pyridines could be achieved at positions 2, 3 or 4 by judicious choice of the carboxylic acid starting material (**40**-**44b**). Finally, quinolines are also amenable for selective deuteration at the position α to the heteroatom (**45**-**46a**). Similar to the analogous protodecarboxylation methodology[25b], pyridine and quinoline carboxylic acids require slightly elevated temperatures (140 °C) to react, however in the presence of 50 equiv of D_2O no additional acid was required.[v]

Table 7. Substrate scope for the deuterodecarboxylation of homo- and hetero-aromatic carboxylic acids [a]



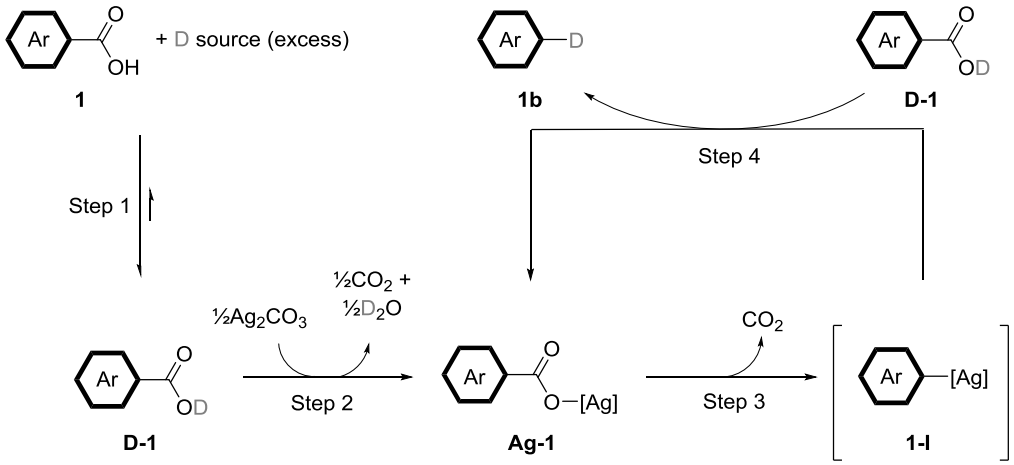
[a]Reaction conditions: all the reactions were carried out under a N_2 atmosphere with 10 mol % Ag_2CO_3, 1.0 equiv of benzoic acid and 50 equiv of D_2O in a 0.2 M DMSO solution at 120 °C for 16 h. Unless otherwise stated, all yields are isolated. [b]Yield determined by ^{1}H NMR analysis using mesitylene or 1,3,5-trimethoxy benzene as an internal standard. Percentage of deuteration indicated in square brackets and was determined by ^{1}H NMR analysis using mesitylene or 1,3,5-trimethoxy benzene as an internal standard. [c]The reaction was carried out at 140 °C.

[v] For the protodecarboxylation of pyridine carboxylic acids 10 mol % AcOH acid was required for high levels of decarboxylation.[25b] The role of the acid has not been elucidated, but it may be required to prevent coordination of the pyridine nitrogen to Ag, or to protodemetallate a stabilised aryl-Ag intermediate. Kozlowski *et al.* observed that in the Pd-catalysed protodecarboxylation of electron-rich benzoic acids the rate limiting step is substrate dependent and can either be decarboxylation or protodemetallation.[51]

The presented method is selective for the carbon bearing the carboxylic acid, even for arenes bearing electron-donating methoxy substituents (**35b**) and for nucleophilic furans **38-39b.** The only instance of H/D scrambling was observed in **36b** where 23% deuteration occurred at the acidic C-H in α to two halogens. The nature of this exchange was not elucidated but may occur via a base or Ag mediated pathway.

2.6. MECHANISTIC DISCUSSION

The proposed mechanism is outlined in Scheme 58, and is analogous to the pathway suggested for the protodecarboxylation reaction;[vi] with the exception of an initial H/D exchange of the acidic hydrogen on the carboxylic acid (Step 1). After the formation of **D-1**, the reaction follows the standard mechanism for the Ag-catalysed decarboxylation, acid/base reaction with Ag_2CO_3 to give the Ag-carboxylate **Ag-1** (Step 2), which loses CO_2 to give the nucleophilic aryl-Ag intermediate **1-I** (Step 3). In this case, the intermediate deuterodemetallates with a molecule of deuterated acid (**D-1**), producing **1b** and regenerating the catalyst (Step 4).

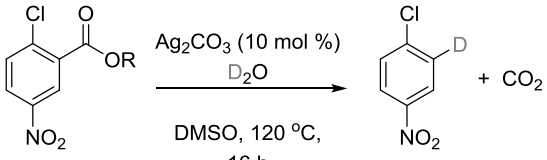


Scheme 58. Proposed mechanism for the deuterodecarboxylation.

As the decarboxylation (Step 3) is thought to be rate determining, it is likely that in the presence of excess D_2O, the carboxylic acid will undergo significant H/D exchange before any decarboxylation has occurred. Therefore once the aryl-Ag intermediate (**1-I**) is produced, the only acid present for the demetallation step should be **D-1**, and quantitative deuteration should be expected. However, the extent of deuteration observed under the optimised conditions varied from 90-98% for the substrates tested. Several reactions were carried out using the optimisation substrate **17e** in an attempt to improve the yield of deuteration (Table 8).

[vi] Chapter 1, Scheme 47.

Table 8. Attempts to improve deuteration yield[a]



R = H, **17**
R = D, **D-17**

17a

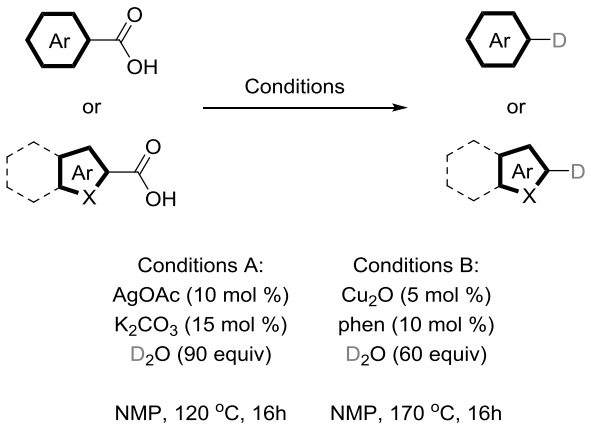
Entry	Substrate	D_2O (equiv)	Comment	D (%)[b]
1	**D-17**	0	Reagents dried under vacuum at 60 °C for 5 hours	58
2	**D-17**	10	"	91
3	**D-17**	50	"	95
4	**17**	10	"	73
6	**17**	50	"	93
7	**17**	50	Ampoule d_6-DMSO	92

[a] Reaction conditions: all the reactions were carried out under a N_2 atmosphere with 10 mol % Ag_2CO_3, 1.0 equiv of substrate and the stated amount of D_2O in a 0.2 M DMSO solution at 120 °C for 16 h. [b]The extent of deuteration was calculated by ^{1}H NMR using mesitylene as an internal standard.

Acid **D-17** was prepared and reacted under the standard conditions. Despite the stringent exclusion of moisture (all reagents were dried under vacuum at 60 °C), only 58% deuteration was observed (Table 8, entry 1). The deuteration could be increased to 91% with 10 equiv of D_2O (Table 8, entry 2); this is a vast improvement in comparison to the analogous reaction with the non-deuterated acid (Table 8, entry 4). However, even with 50 equiv of D_2O, complete deuteration could not be achieved (Table 8, entry 3). As DMSO is weakly acidic (pK_a = 35) and the basicity of the aryl-Ag intermediate is unknown, the reaction was carried out in d_6-DMSO (Table 8, entry 7). The deuteration yield did not increase so it is unlikely that any protodemetallation arises from deprotonation of DMSO.

The experiments in Table 8 show that even with careful exclusion of proton sources and a large excess of deuterium in the reaction media, quantitative deuteration could not be obtained with this substrate. This could indicate that the demetallation step (Step 4) has a significant kinetic isotope effect. On comparison of the IR absorption bands of **D-17**/**17** and D_2O/H_2O; in both cases, the O−D stretch is shifted by ~800cm^{-1} lower in relation to the O−H stretch. A decreased bond vibrational energy indicates a lower zero point energy, thus the activation energy required for the aryl-Ag species to abstract a hydrogen atom by in turn breaking the oxygen-hydrogen bond will be greater for the heavier deuterium atoms. This could rationalise why even trace amounts of H_2O in a large excess of D_2O result in protonation.

2.7. CONCURRENT WORK BY OTHER RESEARCH GROUPS



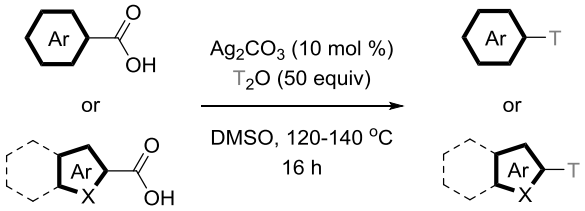
Scheme 59. Independently reported Ag and Cu catalysed deutero-decarboxylation by Gooßen *et al*[20].

During our work into the deutero-decarboxylation of benzoic and heteroaromatic acids, Gooßen *et al.* independently published a comparable methodology, in which they report the selective deuteration of a number of acids using Ag or Cu catalysis.[20] The main drawback of this methodology is the comparative lack of operational simplicity; for the Ag-catalysed protocol, the substrate is heated in an excess of D_2O for 15 mins which is then removed *in vacuo* prior to reaction Moreover, the Cu-catalysed protocol requires three sequential additions of D_2O over 30 mins, during this time the reaction mixture is stirred under nitrogen to promote H/D exchange, before heating. Despite these rigorous precautions, some of their reported deuteration yields are surprisingly low (40-99%).

2.8. CONCLUSIONS AND FUTURE WORK

In conclusion, a high yielding protocol for the selective deuteration of a variety of aromatic acids is presented. The methodology is operationally simple − the benzoic acid is mixed with the catalyst, 50 equiv of D_2O, the vessel purged with N_2 then heated in DMSO. After the reaction, the residual amounts of starting material are easily removed during aqueous workup, affording analytically pure product after solvent evaporation; thus removing the need for column chromatography or distillation. Alternative routes to *ortho*-deutero arenes generally involve the use of strong alkyl-lithium bases and substrates containing a halogen or directing group, however these routes suffer from an inherent limitation in substrate scope. Alternatively, Pd and Ir catalysed methods are reported for mono- and di-*ortho* deuteration. Similar to the Ag(I) catalysed route, these methodologies are mild, permit good regioselectivity, and the use of substrates with functional groups that would not be tolerated in traditional routes. However, when the prices of the catalysts are compared [Ir(acac)(COD) = £75.91mmol^{-1}, $Pd(OAc)_2$ = £14.59 mmol^{-1}, Ag_2CO_3 = £1.36 mmol^{-1}] the Ag(I) catalysed route reported herein is the most economical route.[122] Moreover, due to the

practical and cost effective nature of the protocol, we envisage that this methodology can be utilised for the preparation of drugs with enhanced metabolic stability[94] or adapted towards the tritium-labelling of pharmaceutically relevant molecules to aid drug development and clinical studies.



Scheme 60. The conditions for Ag(I) catalysed deutero decarboxylation could be easily utilised for tritium incorporation.

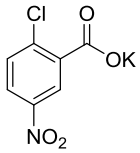
Chapter 2 – Supporting Information

S2.1. GENERAL INFORMATION

Unless otherwise noted, all reactions were carried out under N_2 atmosphere. Anhydrous DMSO, DMF, DMA and all reagents were purchased from commercial suppliers and used without further purification. D_2O (99.9 % D) was purchased from Cambridge Isotope Laboratories Inc. and used without further treatment. IR spectra were recorded using a Bruker Tensor 37 FTIR machine using the thin film method and are quoted in cm^{-1}. Mass spectra were recorded on an Agilent GC-MS, comprising a 6890 GC and 5973 MS. NMR spectra were recorded on a Bruker AV400 or AVIII400 spectrometer. Melting points were obtained using a hot-stage apparatus and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra, recorded at 400 MHz are referenced to the residual solvent peak at 7.26 ppm ($CHCl_3$) or 2.50 ppm (DMSO). ^{2}H NMR spectra, recorded at 61 MHz, are referenced using $CDCl_3$ or *d*$_6$-DMSO as an internal reference. ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the residual solvent peak at 77.16 ppm ($CDCl_3$). Chemical shifts (δ) are quoted in ppm. Impurity peaks observed at 1.43, 1.25 and 0.88 ppm in the ^{1}H NMR and 29.8 ppm in the ^{13}C NMR are likely due to a high order alkanes such as icosane. A superfluous peak observed at 4.73 ppm in the ^{2}H NMR is an artefact due to the spectrometer and not due to a deuterium signal.

S2.2. STARTING MATERIAL PREPARATION

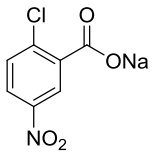
Potassium 2-chloro-5-nitrobenzoate (K-17)[67]



K-17

A solution of *t*-BuOK (1.07 g, 9.5 mmol) in 20 mL of EtOH was added dropwise to a solution of 2-nitro-5-chlorobenzoic acid **17** (2.08 g, 10.0 mmol) in 20 mL of EtOH, and the mixture was stirred at room temperature for 1 h. After this time, the precipitate was filtered, washed with ice cold EtOH (10 mL), then ice cold Et_2O (10 mL) and dried *in vacuo* at 50 ^{o}C to afford **K-17** as a white solid (2.13 g, 89%). ^{1}H NMR (400 MHz, DMSO) δ 8.08 (d, J = 2.8 Hz, 1H), 7.96 (dd, J = 8.7, 2.8 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 165.6, 145.7, 145.4, 136.3, 130.4, 123.0, 121.6.

Sodium 2-chloro-5-nitrobenzoate (Na-17)



Na-17

A solution of *t*-BuONa (0.91 g, 9.5 mmol) in 20 mL of EtOH was added dropwise to a solution of 2-nitro-5-chlorobenzoic acid **17** (2.08 g, 10.0 mmol) in 20 mL of EtOH, and the mixture was stirred at room temperature for 1 h. After this time, the precipitate was filtered, washed with ice cold EtOH (10 mL), then ice cold Et_2O (10 mL) and dried *in vacuo* at 50 ^{o}C to afford **Na-17** as a white solid (2.03 g, 91%). 1H NMR (400 MHz, DMSO) δ 8.16 (d, *J* = 2.9 Hz, 1H), 7.99 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.8, 145.7, 145.5, 136.5, 130.8, 123.7, 122.0.

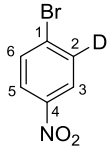
S2.3. GENERAL PROCEDURE FOR THE AG-CATALYSED DEUTERODECARBOXYLATION OF *ORTHO*-SUBSTITUTED (HETERO)AROMATIC ACIDS.

A mixture of acid (0.5 mmol), Ag_2CO_3 (14 mg, 0.05 mmol) and D_2O (452 µL, 25.0 mmol) in anhydrous DMSO (2.5 mL) were stirred for 16 h at 120 °C, in a sealed vessel. After this time, the reaction was partitioned with Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), and then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure product was obtained without further purification.

S2.4.CHARACTERISATION DATA

S2.4.1.Deuterodecarboxylated products

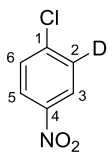
1-Bromo-4-nitro-6-deuterobenzene (14b)



14b

The reaction was carried out following the general procedure with 2-bromo-5-nitrobenzoic acid **14** (0.123 g, 0.5 mmol) to afford **14b** as a white solid (0.096 g, 94%, (90% deuteration)). mp 124- 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.12 (m, 2H), 7.69 (d, *J* = 9.2 Hz, 1.104H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.56 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C4), 132.8 (C6), 132.5 (1:1:1 t, *J* = 17.4 Hz) (C2), 130.0 (C1), 125.2 (C5), 125.1 (C3). IR *v*max (cm^{-1}) 2919 (C−H), 2850 (C−H), 1571 (C=C aryl), 1510 (NO_2), 1336 (NO_2). MS (EI) *m/z* 204 (M^+, 100), 202 (M^+, 100).

1-Chloro-4-nitro-6-deuterobenzene (17b)

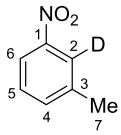


17b

The reaction was carried out following the general procedure with 2-chloro-5-nitrobenzoic acid **17** (0.102 g, 0.5 mmol) to afford **17b** as a pale yellow solid (0.072 g, 91%, (93% deuteration)). m.p 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.20 (m, 2H),

7.52 (d, *J* = 9.2 Hz, 1.067H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.55 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (C4), 141.4 (C1), 129.7 (C6), 129.4 (1:1:1 t, *J* = 27.2 Hz) (C2), 125.1 (C5), 125.0 (C3) IR *v*max (cm^{-1}) 2928 (C−H), 2860 (C−H), 1573 (C=C aryl), 1519 (NO_2), 1342 (NO_2). MS (EI) *m/z* 158 (M^+, 100).

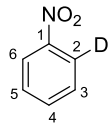
3-Nitro-2-deuterotoluene (23b)



23b

The reaction was carried out following the general procedure with 2-methyl-6-nitrobenzoic acid **23** (0.091g, 0.5 mmol) to afford **23b** as a pale yellow oil (0.057g, 82%, (97% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1.035H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H) 2.47 (s, 3H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 8.07 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (C1), 139.8 (C3), 135.4 (C5), 129.2 (C4), 123.7 (1:1:1 t, *J* = 25.6 Hz) (C2), 120.8 (C6), 21.3 (C7). IR *v*max (cm^{-1}) 2924 (C−H), 2864 (C−H), 1521 (NO_2), 1346 (NO_2). MS (EI) *m/z* 138 (M^+, 100).

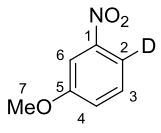
1-Nitro-2-deuterobenzene (24b)



24b

The reaction was carried out following the general procedure with 2-nitrobenzoic acid **24** (0.084 g, 0.5 mmol) to afford **24b** as a yellow oil (0.58 g, 93%, (98% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.4, 0.8 Hz, 1.025H), 7.70 (td, *J* = 7.6, 1.2 Hz, 1H), 7.56 (m, 2H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 8.16 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3 (C1), 134.7 (C4), 129.4 (C5), 129.3 (C3), 123.6 (C6), 123.4 (1:1:1 t, *J* = 17.2 Hz) (C2). IR *v*max (cm^{-1}) 2923 (C−H), 2855 (C−H), 1697 (C=C aryl), 1547 (NO_2). MS (EI) *m/z* 124 (M^+, 100).

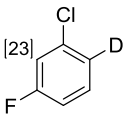
1-Methoxy-3-nitro-4-deuterobenzene (35b)



35b

The reaction was carried out following the general procedure with 4-methoxy-2-nitrobenzoic acid **35** (0.099g, 0.5 mmol) to afford **35b** as a pale yellow solid (0.075 g, 97%, (95% deuteration)). m.p.: 35-37 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 0.050H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.42 (d, 8.4 Hz, 1H), 7.21 (dd, 8.4, 2.8 Hz, 1H), 3.88 (s, 3H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.87 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (C5), 149.4 (C1), 129.9 (C3), 121.3 (C4), 115.6 (1:1:1 t, *J* = 26.2 Hz) (C2), 108.3 (C6). 55.9 (C7). IR *v*max (cm^{-1}) 2936 (C−H), 2845 (C−H), 1523 (NO_2), 1347 (NO_2), 1235 (C−O aromatic), 1036 (C−O aliphatic). MS (EI) *m/z* 154 (M^+, 100).

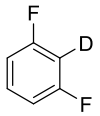
1-chloro-3-fluoro-6-deuterobenzene (36b)



36b

The reaction was carried out following the general procedure in a sealed vessel with 2-chloro-4-fluorobenzoic acid **36** (0.017 g, 0.1 mmol)) and d_6-DMSO (0.5 mL) to afford **36b** (89%, (94% deuteration (C6) and 23% deuteration (C2)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.43 (app t, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 0.059 H), 7.17 (ddd, *J* = 2.3, 8.6 Hz, 1H). ^{2}H NMR (61 MHz, d_6-DMSO) δ 7.74 (1D, s, C2), 7.14 (1D, s, C6). MS (EI) *m/z* 115 (M^+, 100).

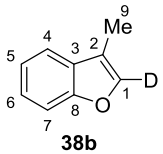
1,5-Difluoro-6-deuterobenzene (37b)



37b

The reaction was carried out following the general procedure in a sealed vessel with 2,6-difluorobenzoic acid **37** (0.016 g, 0.1 mmol)) and d_6-DMSO (0.5 mL) to afford **37b** (97%, (94% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.44 (app quin, *J* = 7.6 Hz, 1H,), 7.11-7.17 (m, 0.062H), 7.05 (t, *J* = 6.8 Hz, 2H). ^{2}H NMR (61 MHz, d_6-DMSO) δ 7.23 (1D, s). MS (EI) *m/z* 115 (M^+, 100).

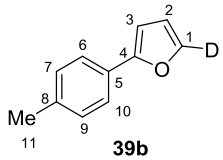
2-Deutero-3-methylbenzofuran (38b)



38b

The reaction was carried out following the general procedure with 3-methylbenzofuran-2-carboxylic acid **38** (0.088g, 0.5 mmol) to afford **38b** as an orange-red oil (0.54 g, 81%, (93% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H); 7.48 (d, *J* = 7.6 Hz, 1H); 7.42 (s, 0.075H); 7.31 (t, *J* = 7.6 Hz, 1H); 7.26 (t, *J* = 7.6 Hz, 1H); 2.27 (s, 3H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.45 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (C8), 141.2 (1:1:1 t, *J* = 30.5 Hz) (C1), 129.2 (C3), 124.2 (C6), 122.3 (C5), 119.5 (C4), 115.5 (C2), 111.4 (C7), 7.9 (C9). IR *v*max (cm^{-1}) 2923 (C−H), 2855 (C−H), 1461 (C=C aryl), 1218 (C−O), 1122 (C−O). MS (EI) *m/z* 133 (M^+, 100).

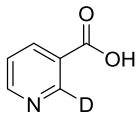
2-Deutero-5-(*p*-tolyl)furan (39b)



39b

The reaction was carried out following the general procedure with 5-(*p*-tolyl)furan-2-carboxylic acid **39** (0.088g, 0.5 mmol) to afford **39b** as an yellow oil (0.64 g, 81%, (95% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H); 7.46 (dd, *J* = 2.0, 0.8 Hz, 0.054H); 7.21 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 3.2 Hz, 1H,); 6.47 (d, *J* = 3.2 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.49. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (C4), 141.6 (1:1:1 t, *J* = 31.1 Hz) (C1), 137.3 (C8), 129.5 (C7 & 9), 128.5 (C5), 123.9 (C6 & 10), 111.5 (C3), 104.3 (C2), 21.4 (C11). IR *v*max (cm^{-1}) 2919 (C−H), 2852 (C−H), 1458 (C=C aryl), 1208 (C−O); MS (EI) *m/z* 159 (M^+, 100).

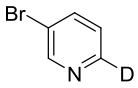
2-deutero-3-pyridinecarboxylic acid (40b)



40b

The reaction was carried out following the general procedure in a sealed vessel with pyridine-2,3-dicarboxylic acid **40** (0.017 g, 0.1 mmol)) and d_6-DMSO (0.2 mL) to afford **40b** (91%, (95% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.05 (s, 0.054H): 8.77 (d, *J* = 1.6 Hz, 1H); 8.27 (d, *J* = 7.6 Hz, 1H); 7.54 (t, 6.2 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 10.19 (1D, s).

3-Bromo-6-deuteropyridine (41b)



41b

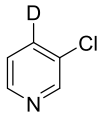
The reaction was carried out following the general procedure in a sealed vessel with 5-bromopicolinic acid **41** (0.016 g, 0.1 mmol)) and d_6-DMSO (0.2 mL) to afford **41a** (36%, (91% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.67 (s, 1H), 8.55 (d, *J* = 4.4 Hz, 0.088H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.32 (d, 8.4 Hz, 1H).

2-Chloro-3-deuteropyridine (42b)

42b

The reaction was carried out following the general procedure in a sealed vessel with 2-chloronicotinic acid **42** (0.016 g, 0.1 mmol)) and d_6-DMSO (0.5 mL) to afford **42b** (>99%, (95% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.39 (dd, *J* = 4.8, 2.0 Hz, 1H); 7.84 (d, *J* = 7.2 Hz, 1H); 7.48 (d, *J* = 8.0 Hz, 0.048H); 7.40 (dd, J = 7.6, 4.8 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.77 (1D, s). MS (EI) *m/z* 114 (M^+, 100).

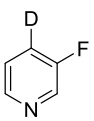
3-Chloro-4-deuteropyridine (43b)



43b

The reaction was carried out following the general procedure in a sealed vessel with 3-chloroisonicotinic acid **43** (0.016 g, 0.1 mmol)) and d_6-DMSO (0.5 mL) to afford **43b** (48%, (92% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.68 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 0.083 H), 7.35 (d, *J* = 4.4 Hz, 1H).

3-Fluoro-4-deuteropyridine (44b)

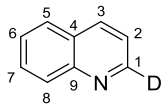


44b

The reaction was carried out following the general procedure in a sealed vessel with 3-fluoroisonicotinic acid **44** (0.014 g, 0.1 mmol) and d_6-DMSO (0.5 mL) to afford **44b** (81%, (95% deuteration)) as calculated by ^{1}H NMR using mesitylene as the internal standard. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.46 (s, 1H); 8.39 (dd, *J* = 4.8, 2.0 Hz, 1H); 7.60 (dddd, *J* = 8.8, 8.8, 2.8,

1.2 Hz, 0.053H), 7.43 (t, *J* = 4.8 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 7.98 (1D, s). MS (EI) *m/z* 98 (M^+, 100).

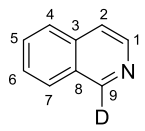
2-Deuteroquinoline (45b)



45b

The reaction was carried out following the general procedure with 2-quinolinecarboxylic acid **45** (0.087 g, 0.5 mmol)) to afford **45b** as a colourless oil (0.060 g, 93%, (97% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, 4.0, 1.6 Hz, 0.029H); 8.11 (t, 7.2 Hz, 2H); 7.79 (d, 8.0 Hz, 1H,); 7.70 (t, 7.6 Hz, 1H); 7.52 (t, 7.4 Hz, 1H); 7.36 (d, 8.0 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 8.95 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (1:1:1 t, *J* = 27.3 Hz) (C1), 148.4 (C9), 136.1 (C3), 129.6 (C7), 129.5 (C8), 128.4 (C4), 127.9 (C5), 126.6 (C6), 121.0 (C2). IR *v*max (cm^{-1}) 2928 (C−H), 2856 (C−H), 1625 (C=C aryl), 1584 (C=C aryl), 1217 (C−N). MS (EI) *m/z* 130 (M^+, 100).

1-Deuteroisoquinoline (46b)

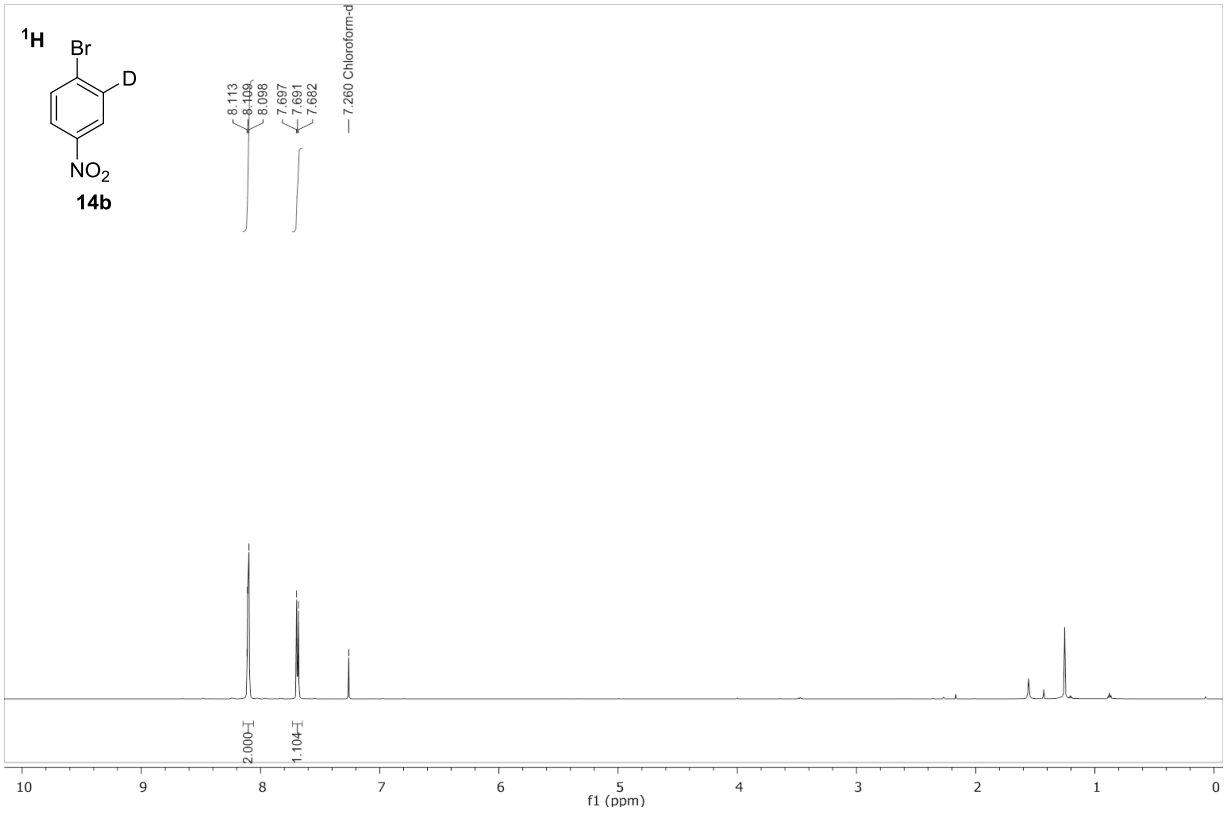


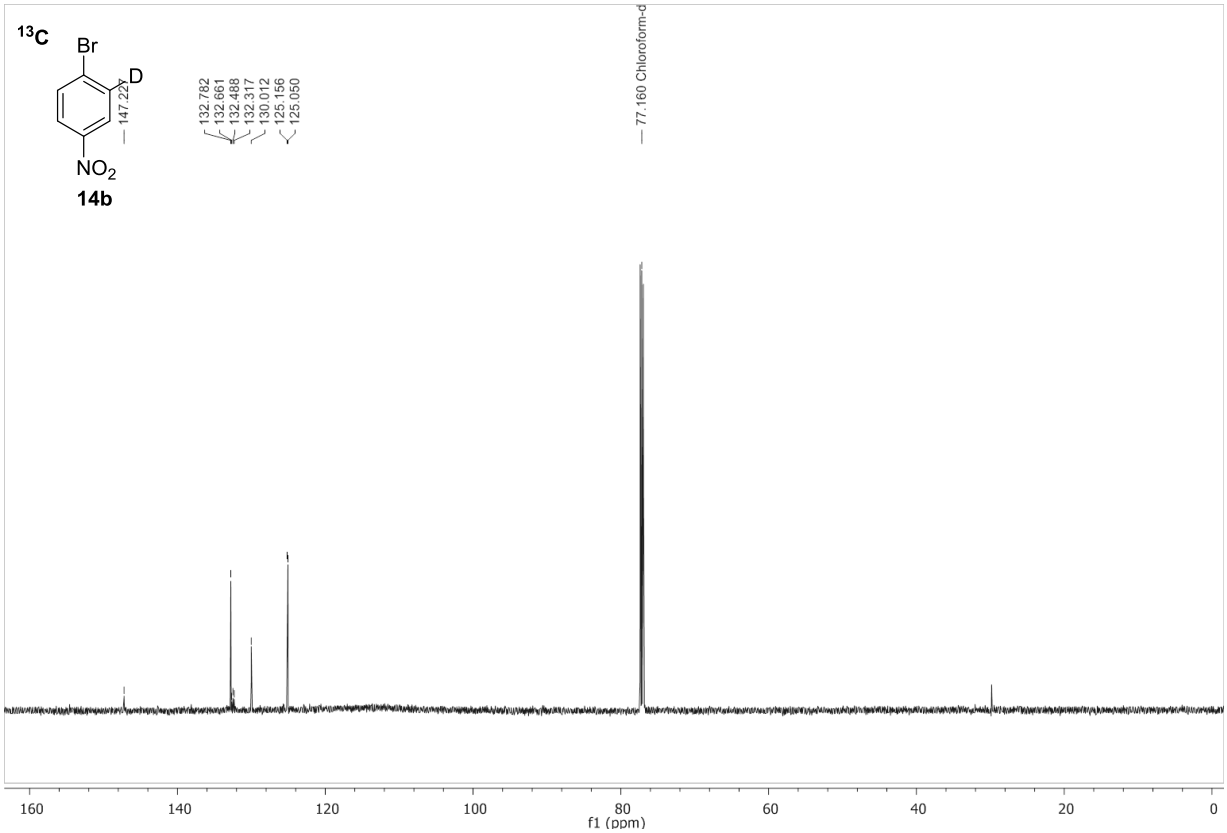
46a

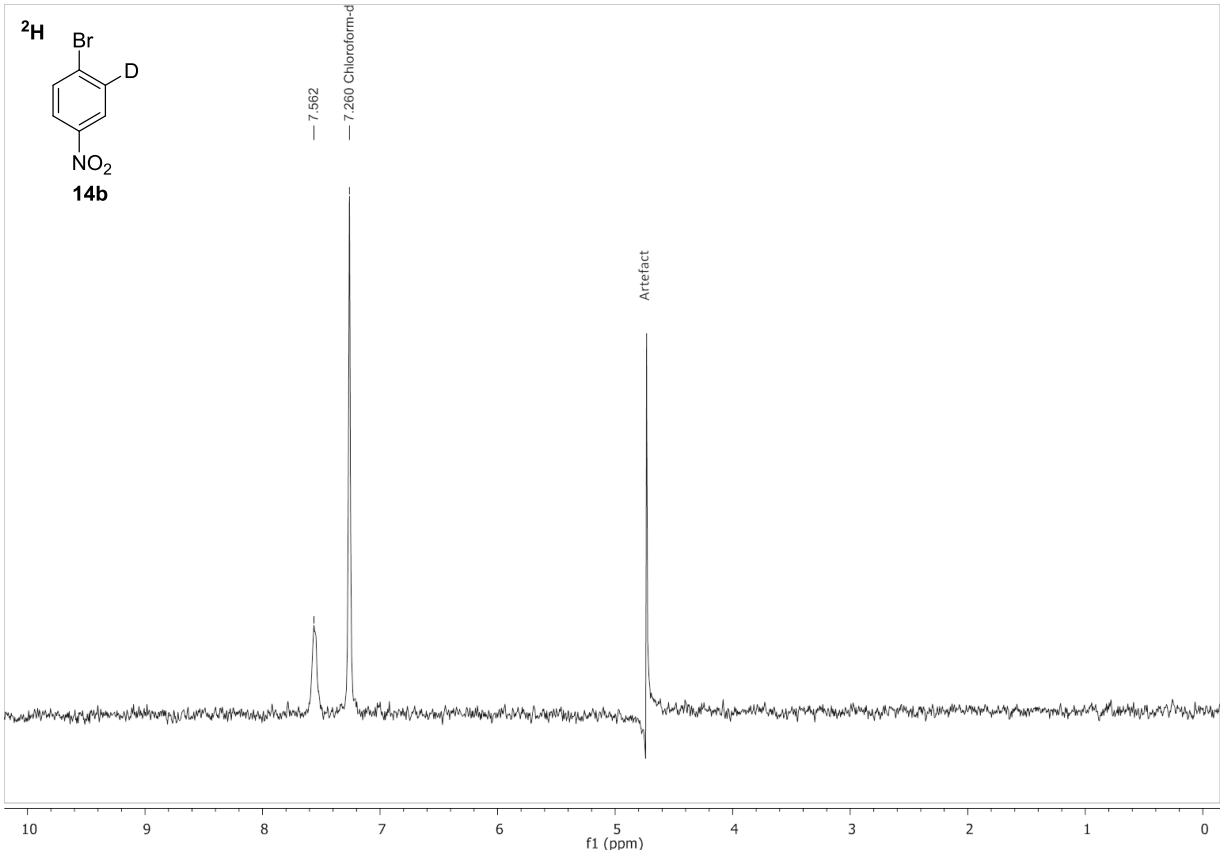
The reaction was carried out following the general procedure with 1-isoquinolinecarboxylic acid **46** (0.087 g, 0.5 mmol)) to afford **46b** as a colourless oil (0.059 g, 91%, (98% deuteration)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 0.023H); 8.52 (d, 6.0 Hz, 1H); 7.95 (d, 8.0 Hz, 1H); 7.79 (t, 7.6 Hz, 1H); 7.67 (t, 7.6 Hz, 1H); 7.63 (d, 5.6 Hz, 1H); 7.58 (t, 7.4 Hz, 1H). ^{2}H NMR (61 MHz, $CDCl_3$) δ 9.29 (1D, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (1:1:1 t, *J* = 31.1 Hz) (C9), 143.1 (C1), 135.9 (C3), 130.4 (C5), 128.7 (C5), 127.7 (C7), 127.3 (C6), 126.5 (C4), 120.5 (C2). IR *v*max (cm^{-1}) 2916 (C−H), 2849 (C−H), 1626 (C=C aryl), 1463 (C=C aryl), 1255 (C−N). MS (EI) *m/z* 130 (M^+, 100).

S2.4.2. Spectra of deuterated compounds

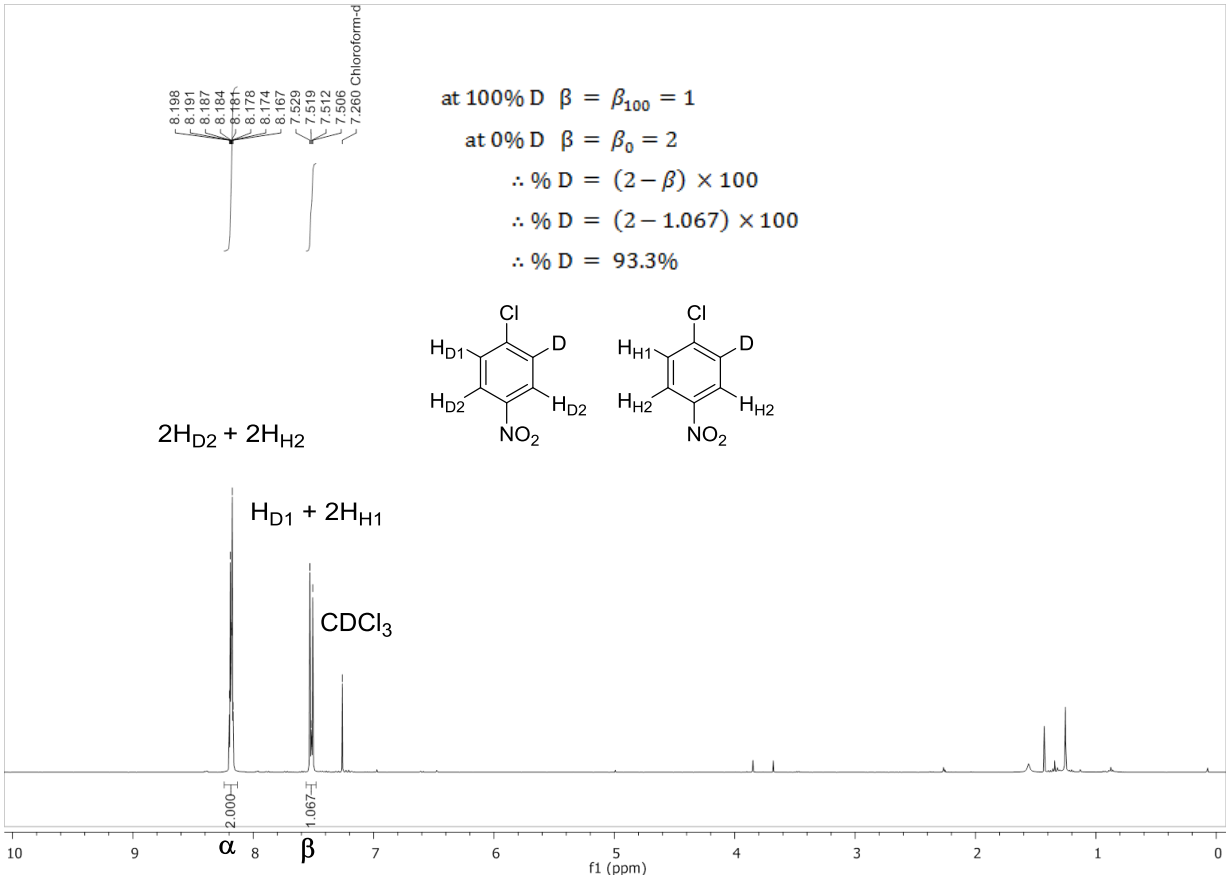
1-Bromo-4-nitro-6-deuterobenzene (14b)

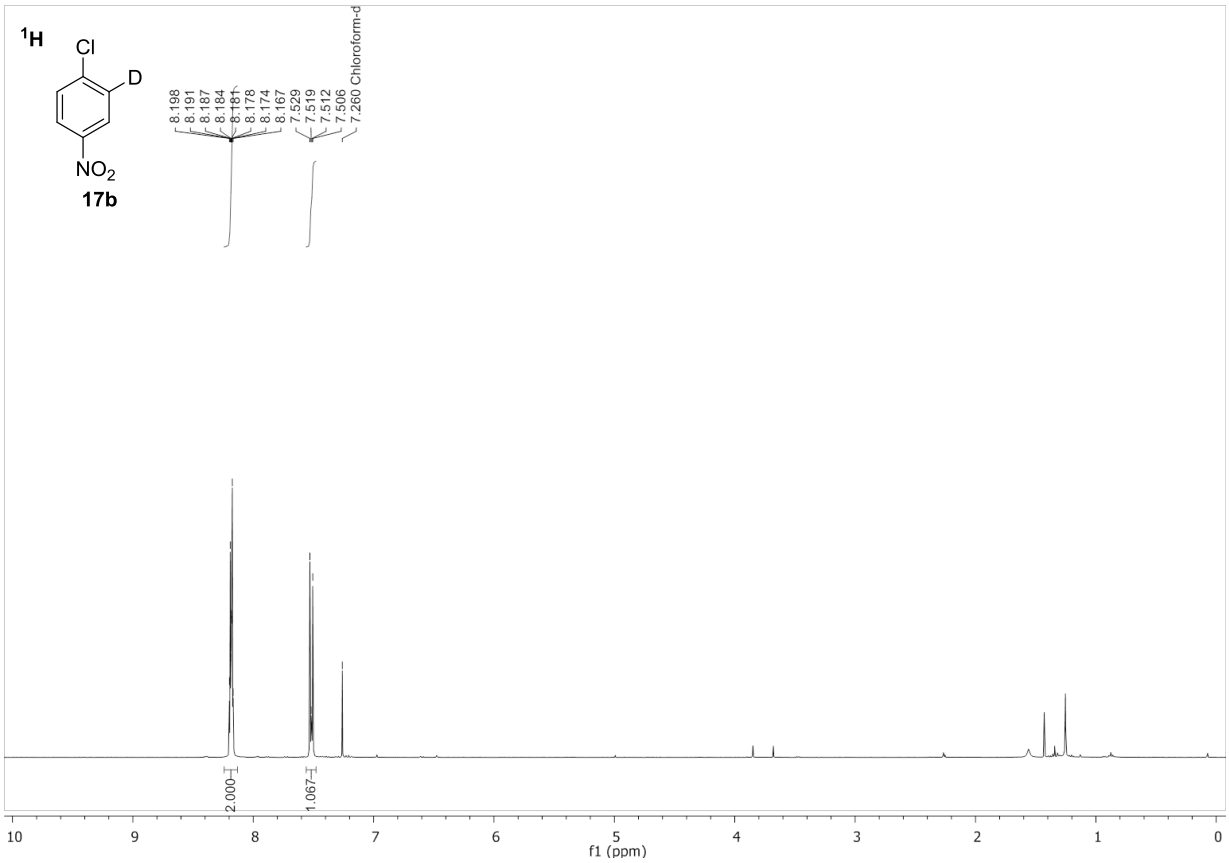


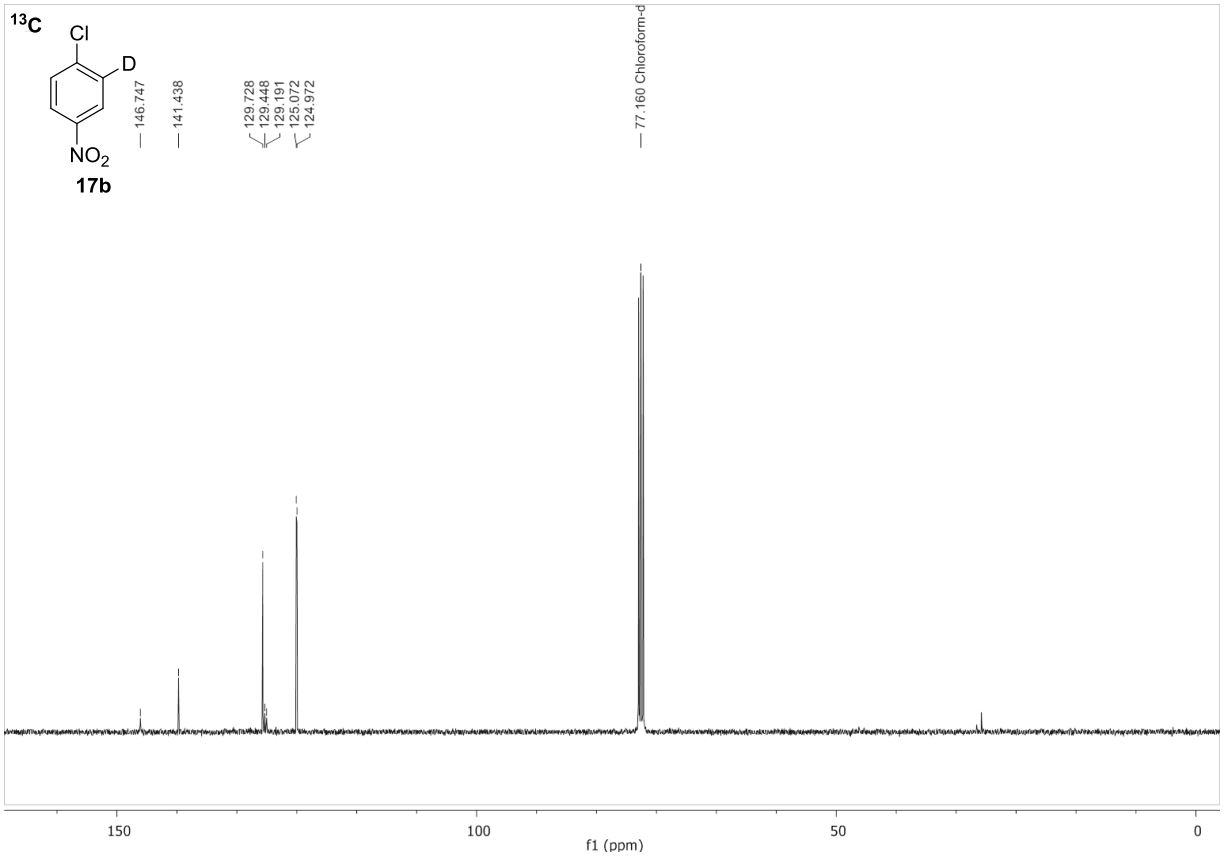


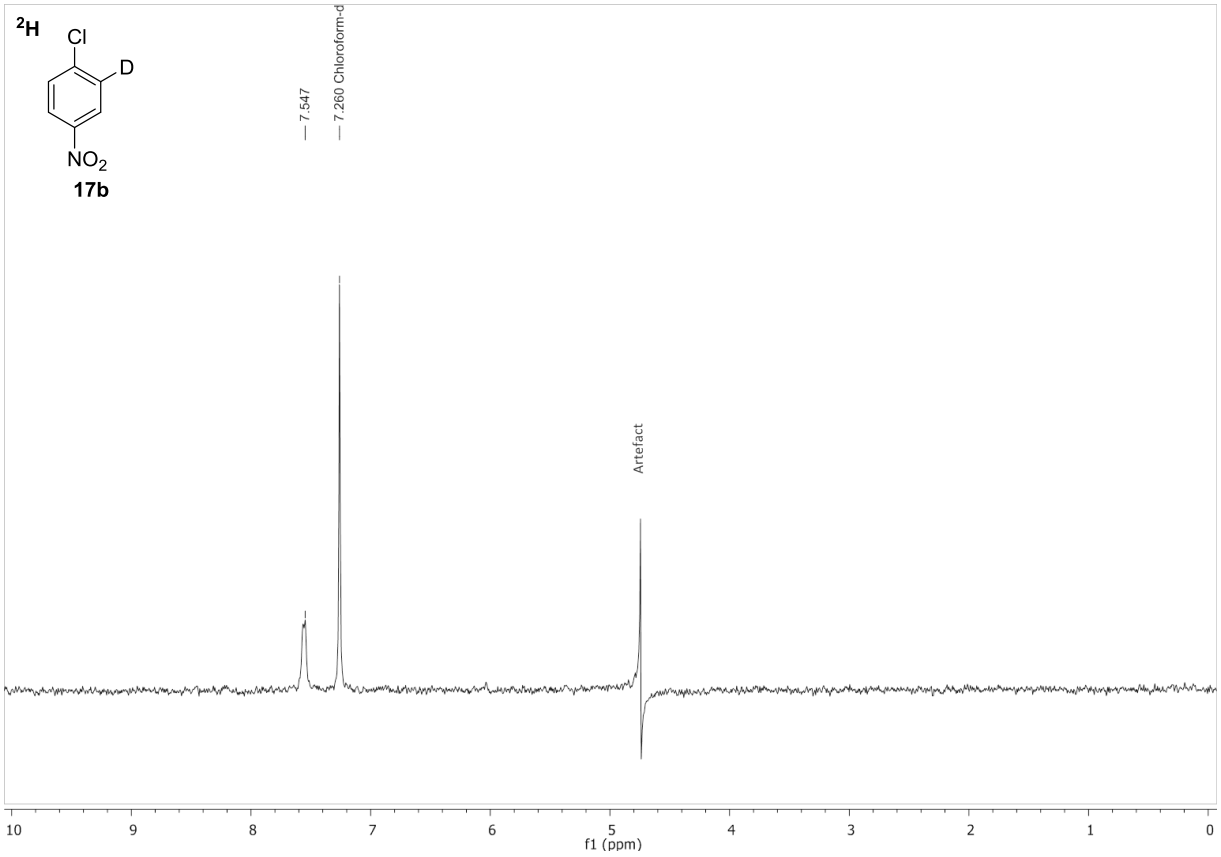


1-Chloro-4-nitro-6-deuterobenzene (17b)

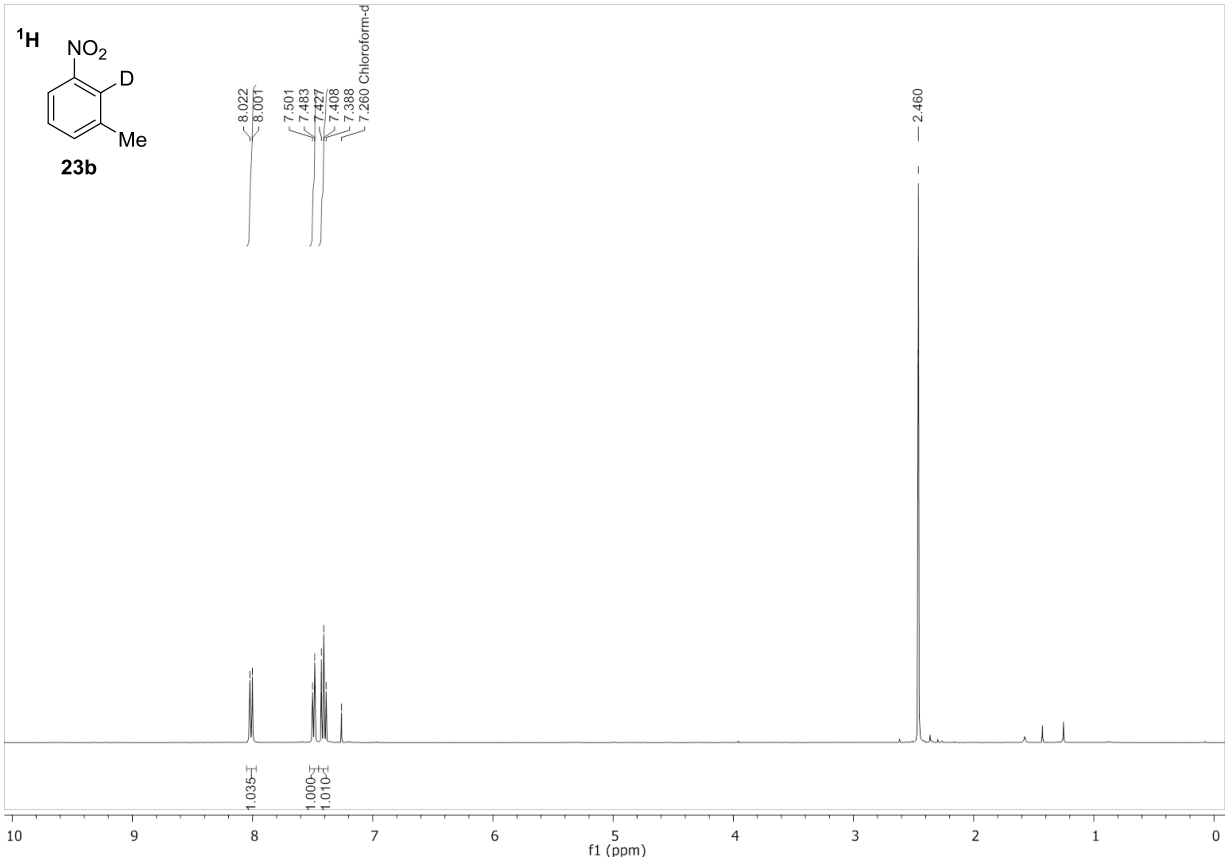


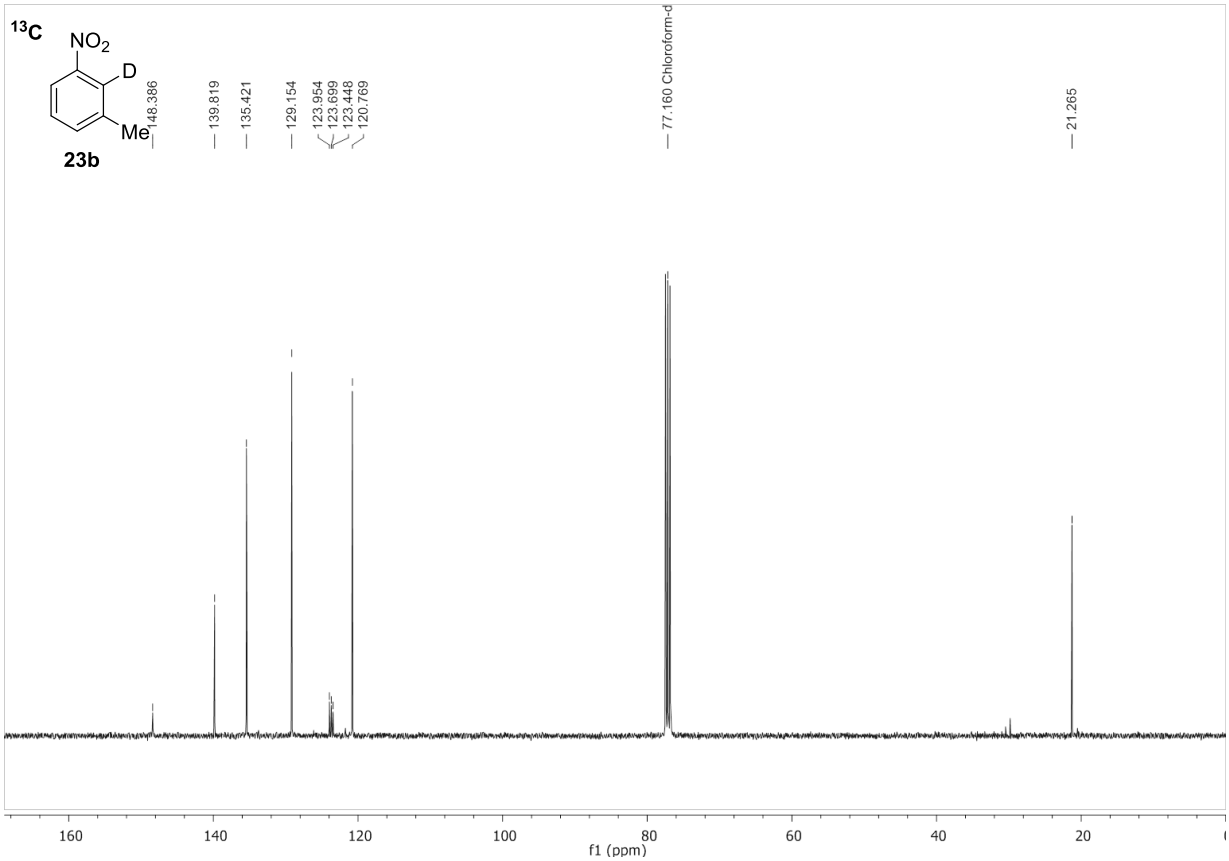

1H
Cl
D
NO2
17b
8.198
8.191
8.187
8.184
8.181
8.178
8.174
8.167
7.529
7.519
7.512
7.506
7.260 Chloroform-d
2.000
1.067
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

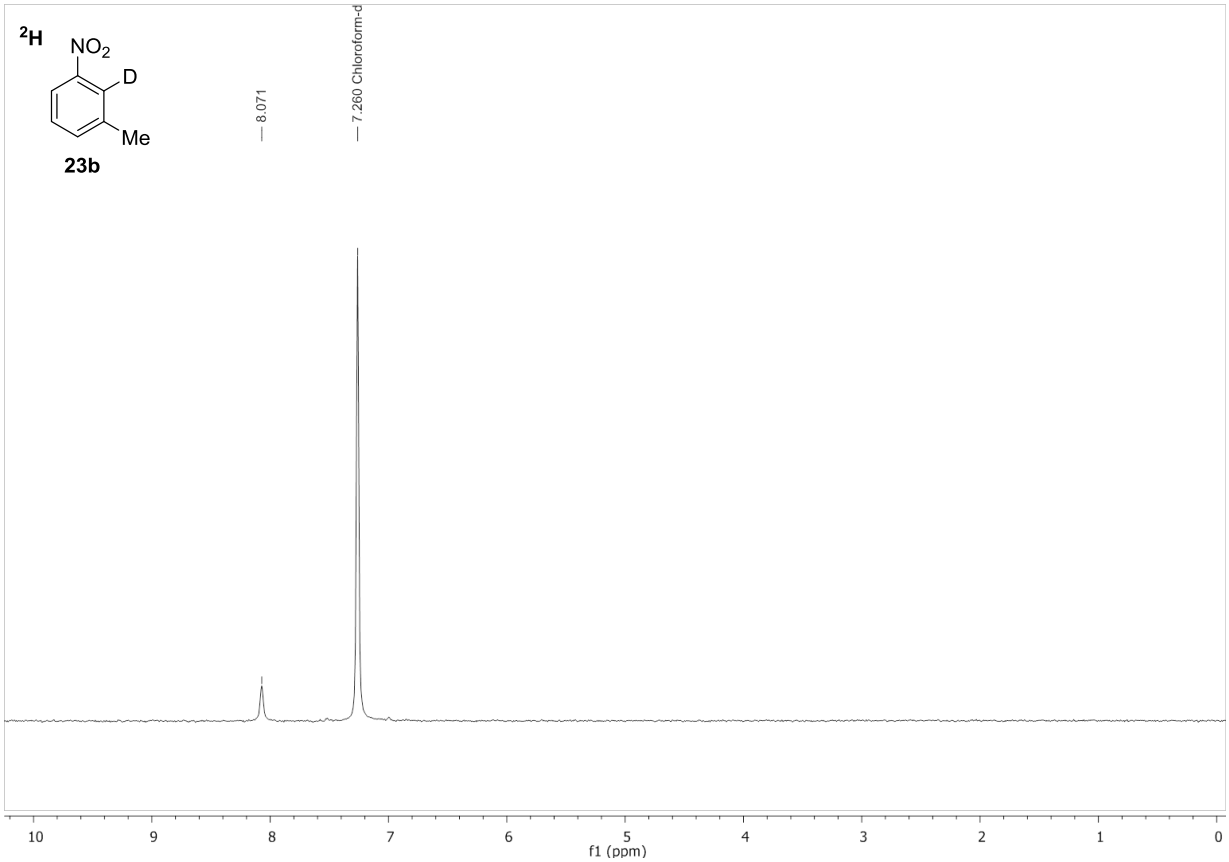

13C
Cl
D
NO2
17b
146.747
141.438
129.728
129.448
129.191
125.072
124.972
77.160 Chloroform-d
150
100
50
0
f1 (ppm)



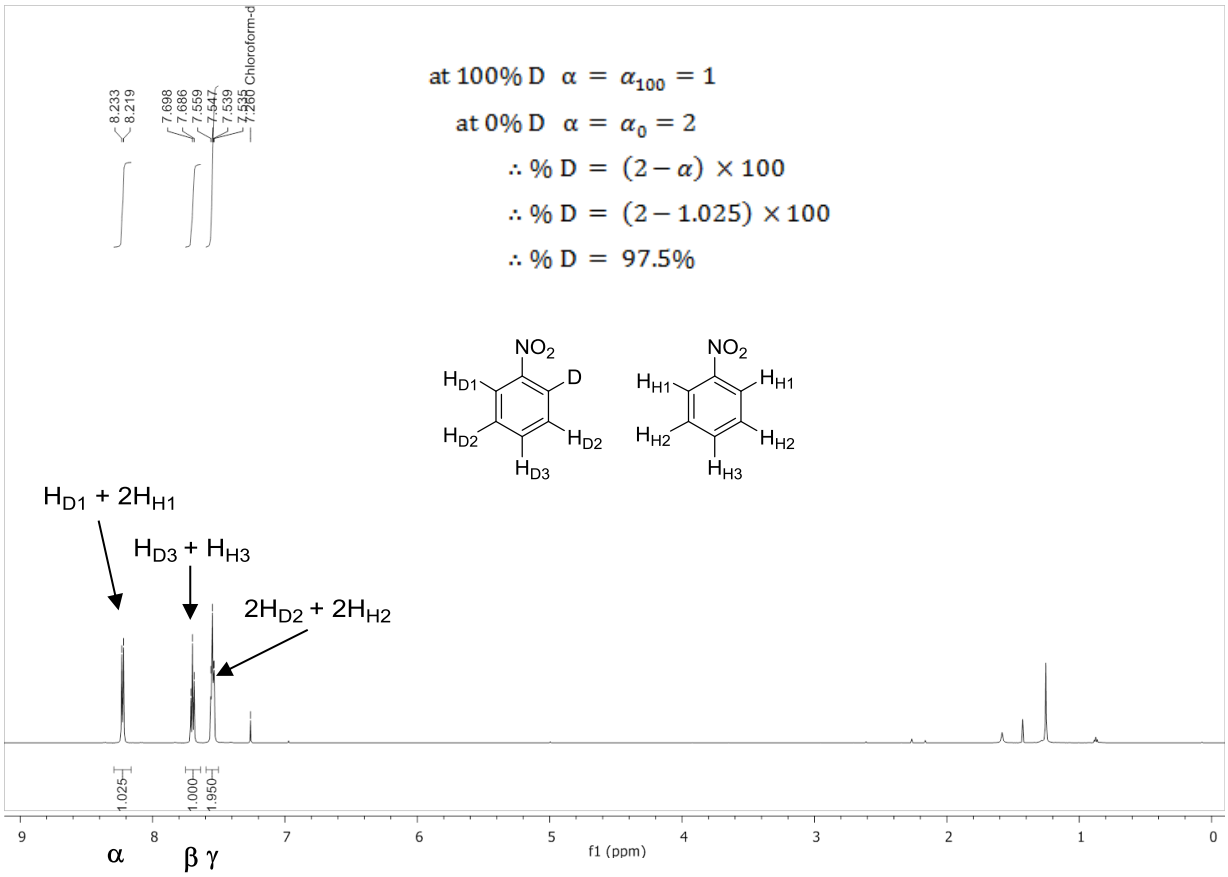
3-Nitro-2-deuterotoluene (23b)

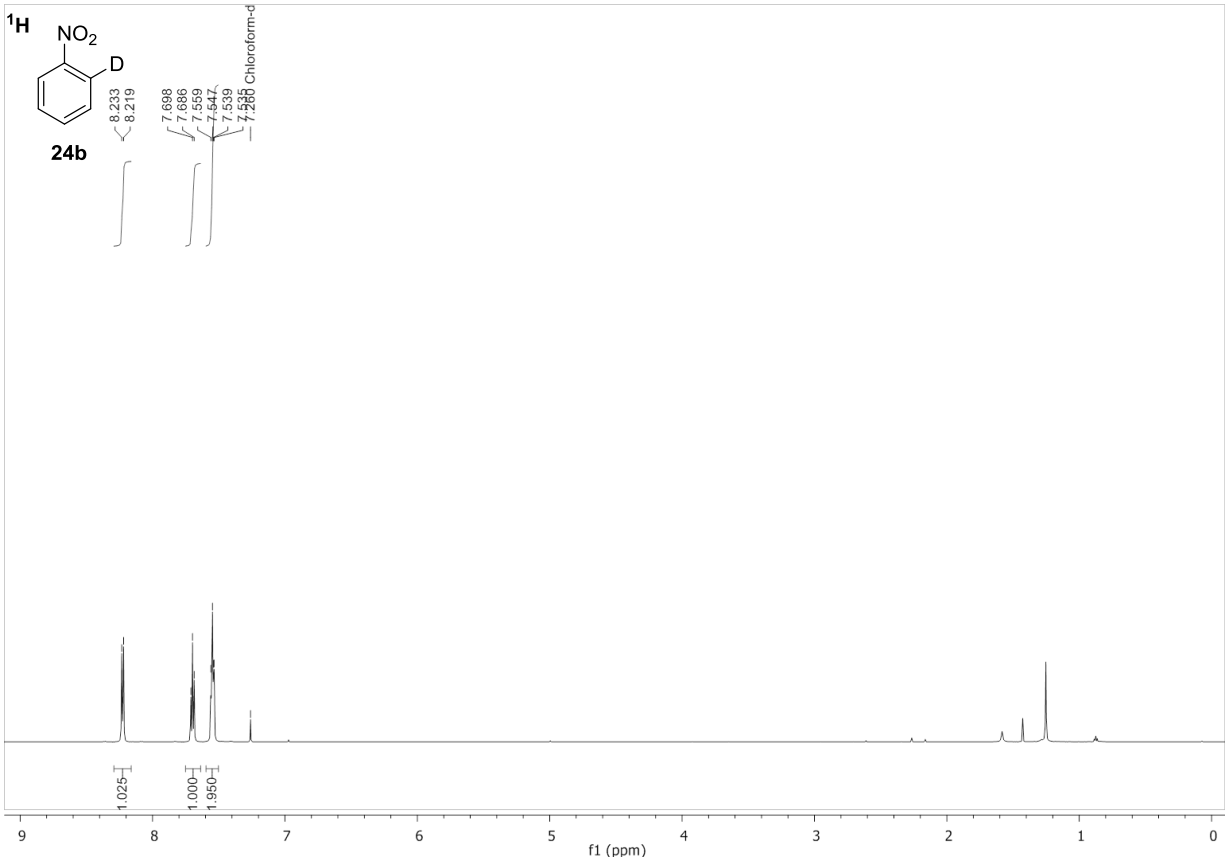


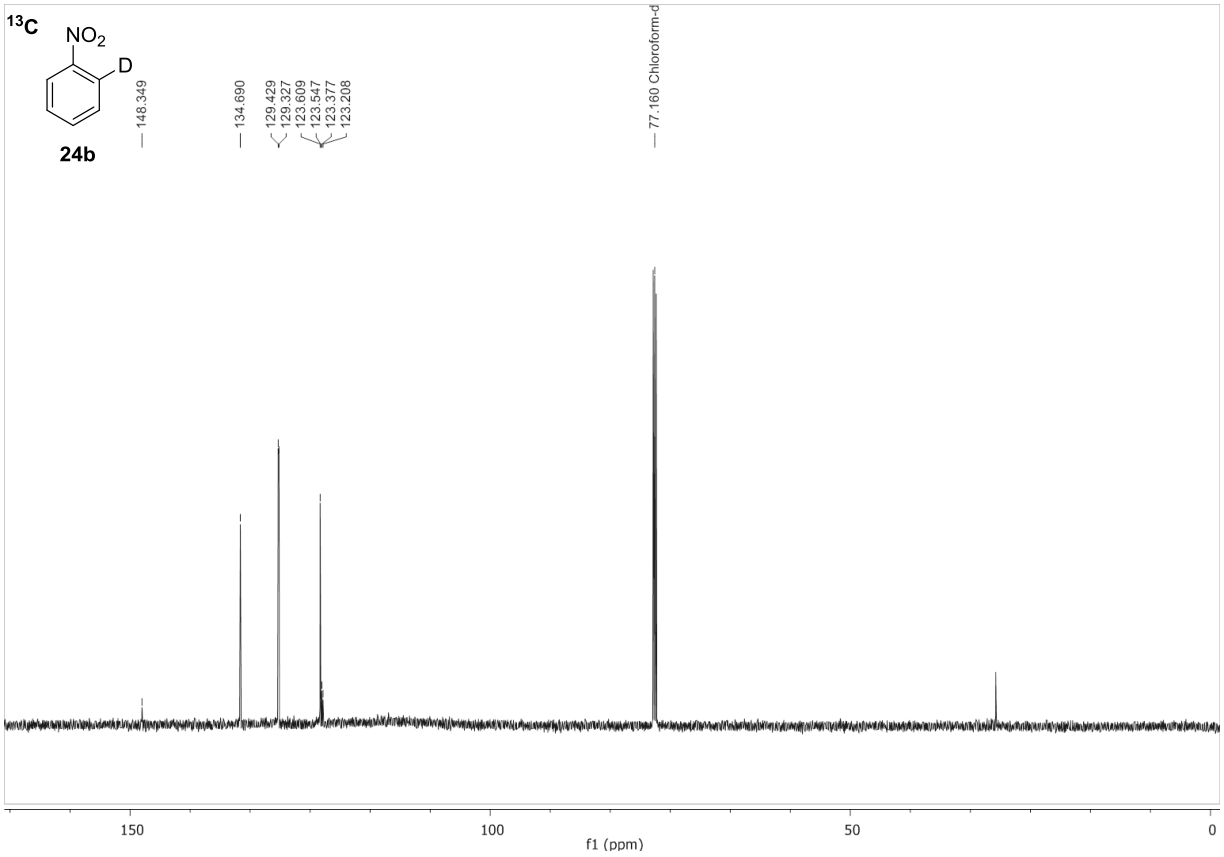

13C
NO2
D
Me
23b
148.386
139.819
135.421
129.154
123.954
123.699
123.448
120.769
77.160 Chloroform-d
21.265
160
140
120
100
80
60
40
20
f1 (ppm)

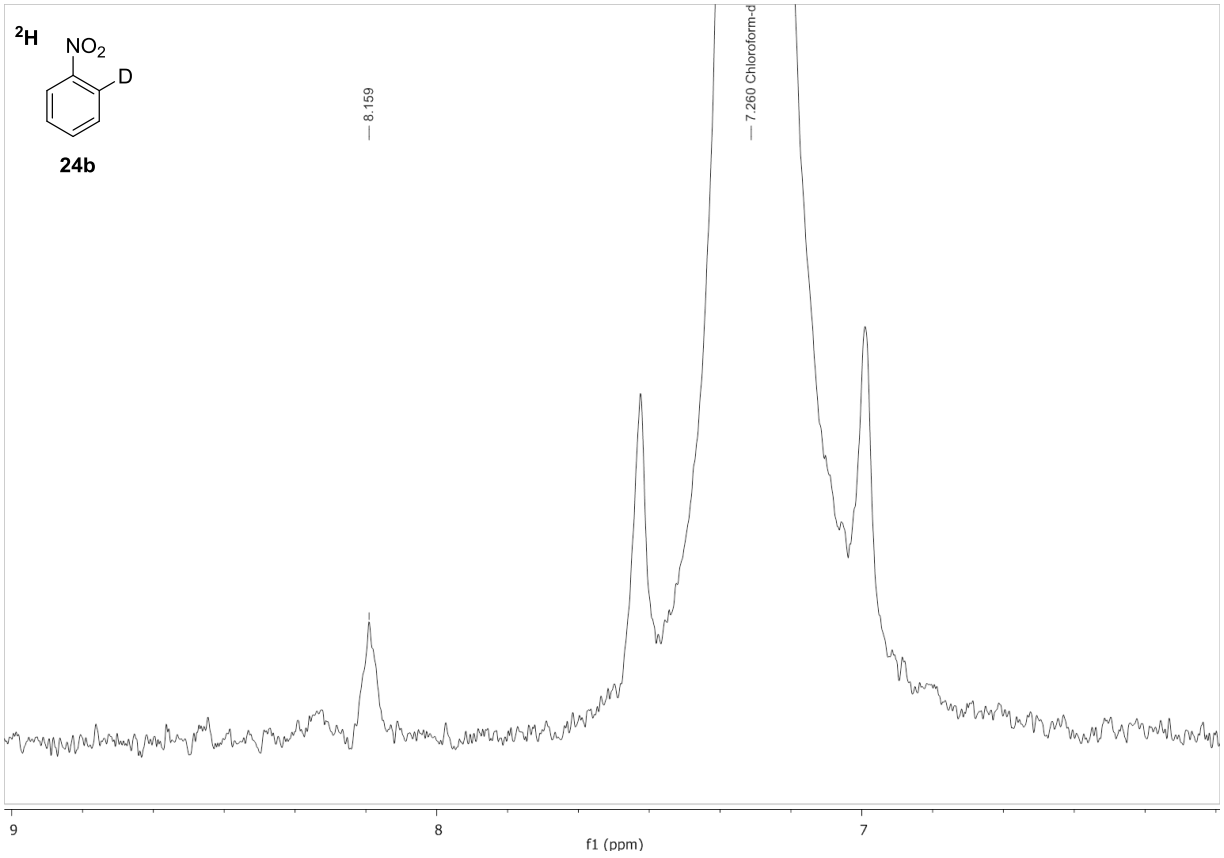

2H
NO2
D
Me
23b
8.071
7.260 Chloroform-d
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

1-Nitro-2-deuterobenzene (24b)

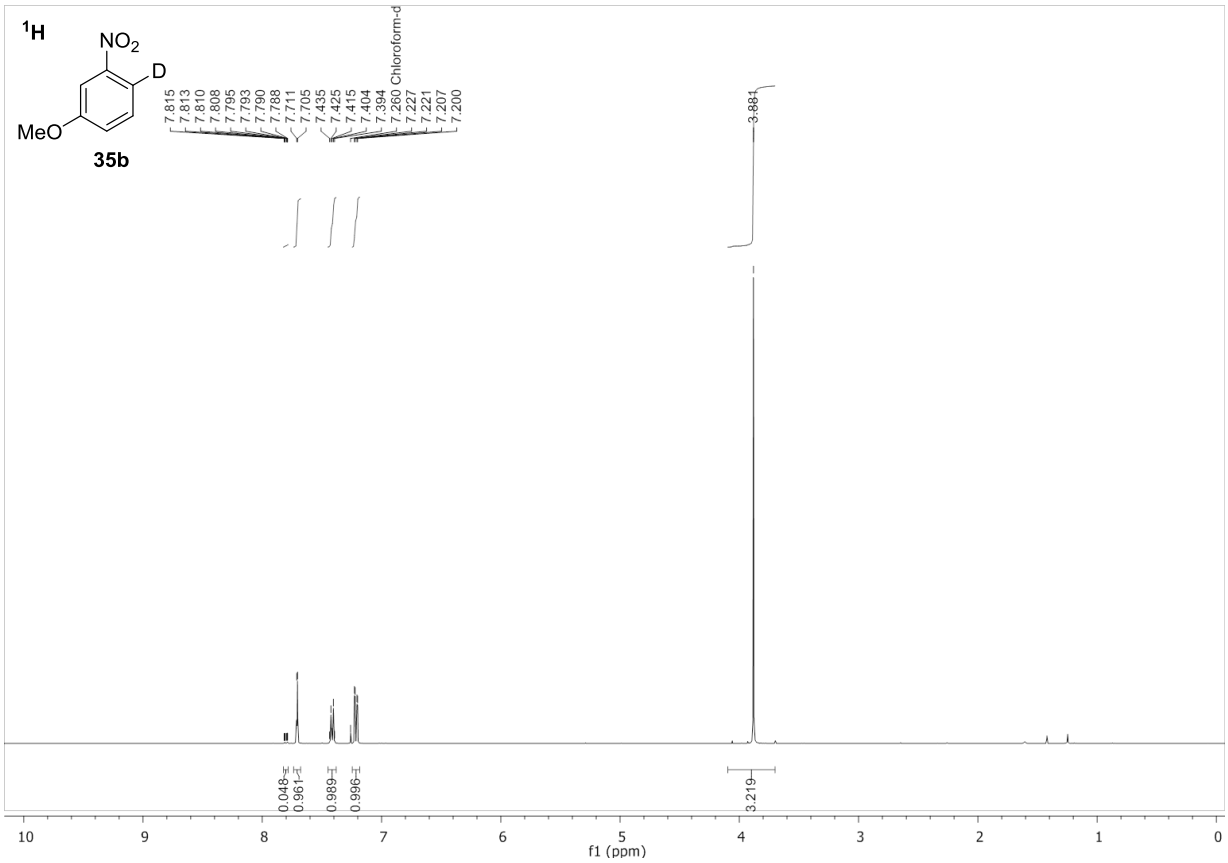


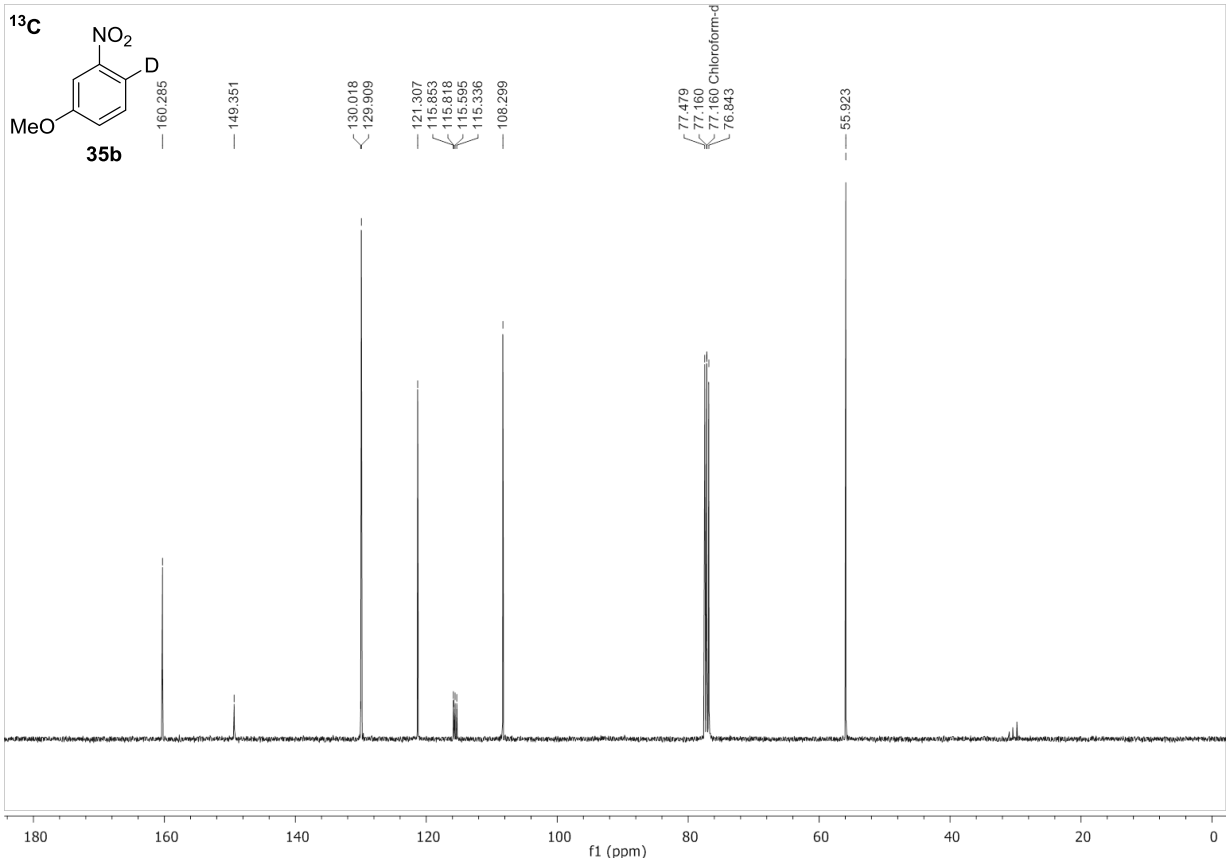


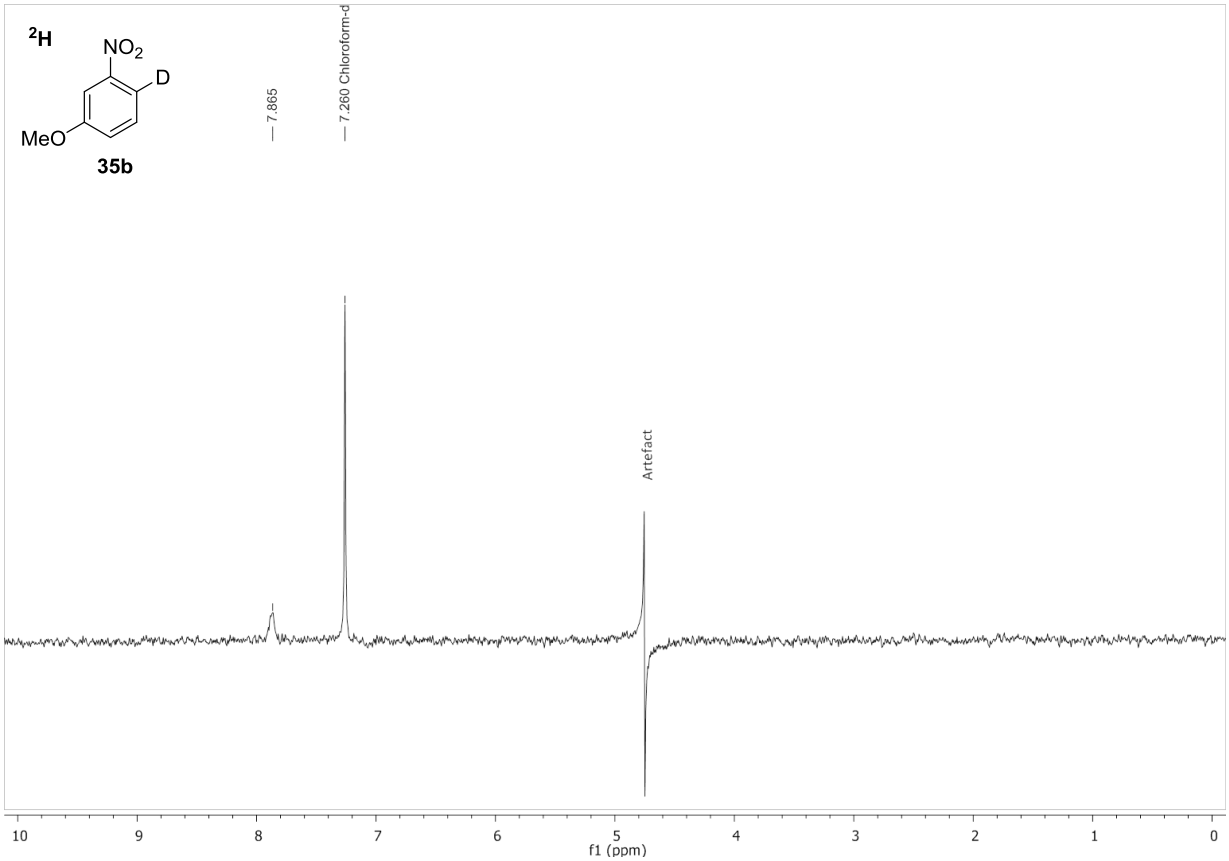

13C
NO2
D
24b
148.349
134.690
129.429
129.327
123.609
123.547
123.377
123.208
77.160 Chloroform-d
150
100
50
0
f1 (ppm)


2H
NO2
D
24b
8.159
7.260 Chloroform-d
9
8
7
f1 (ppm)

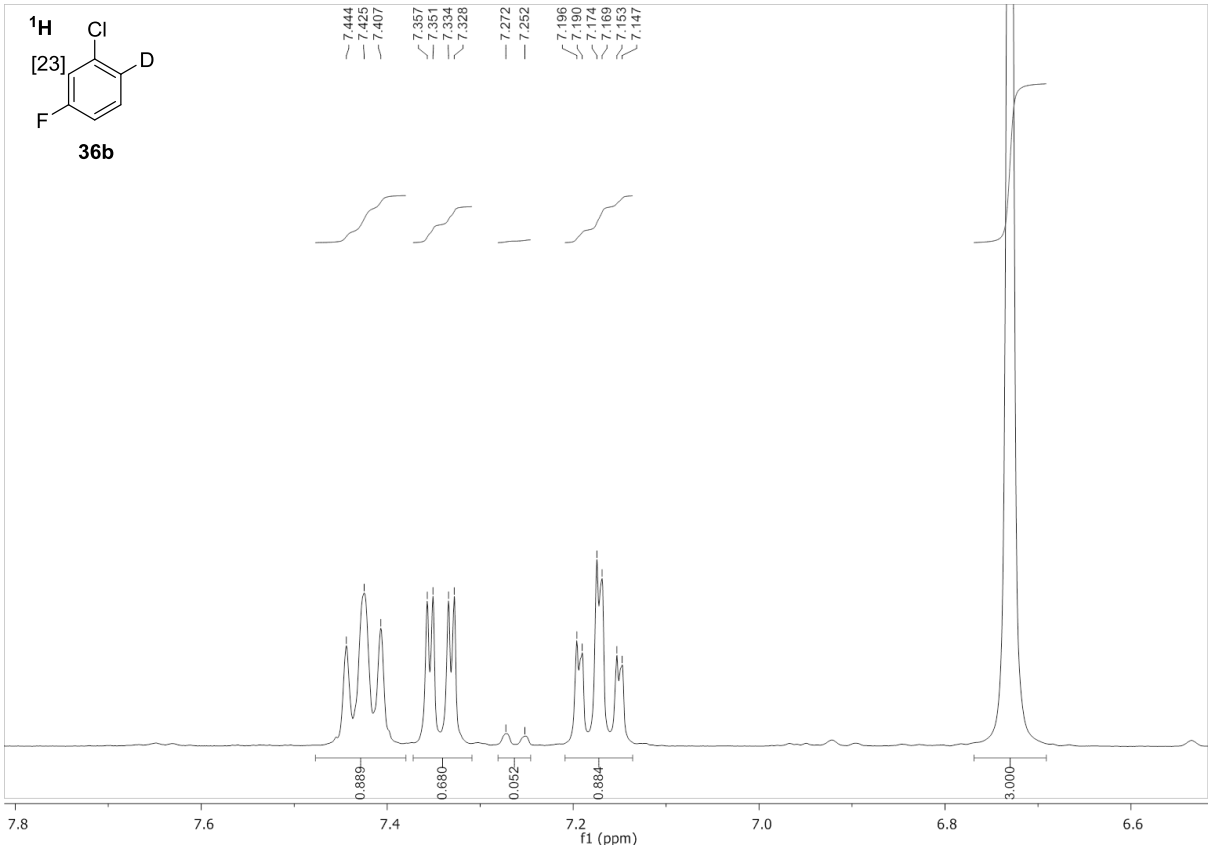
1-Methoxy-3-nitro-4-deuterobenzene (35b)

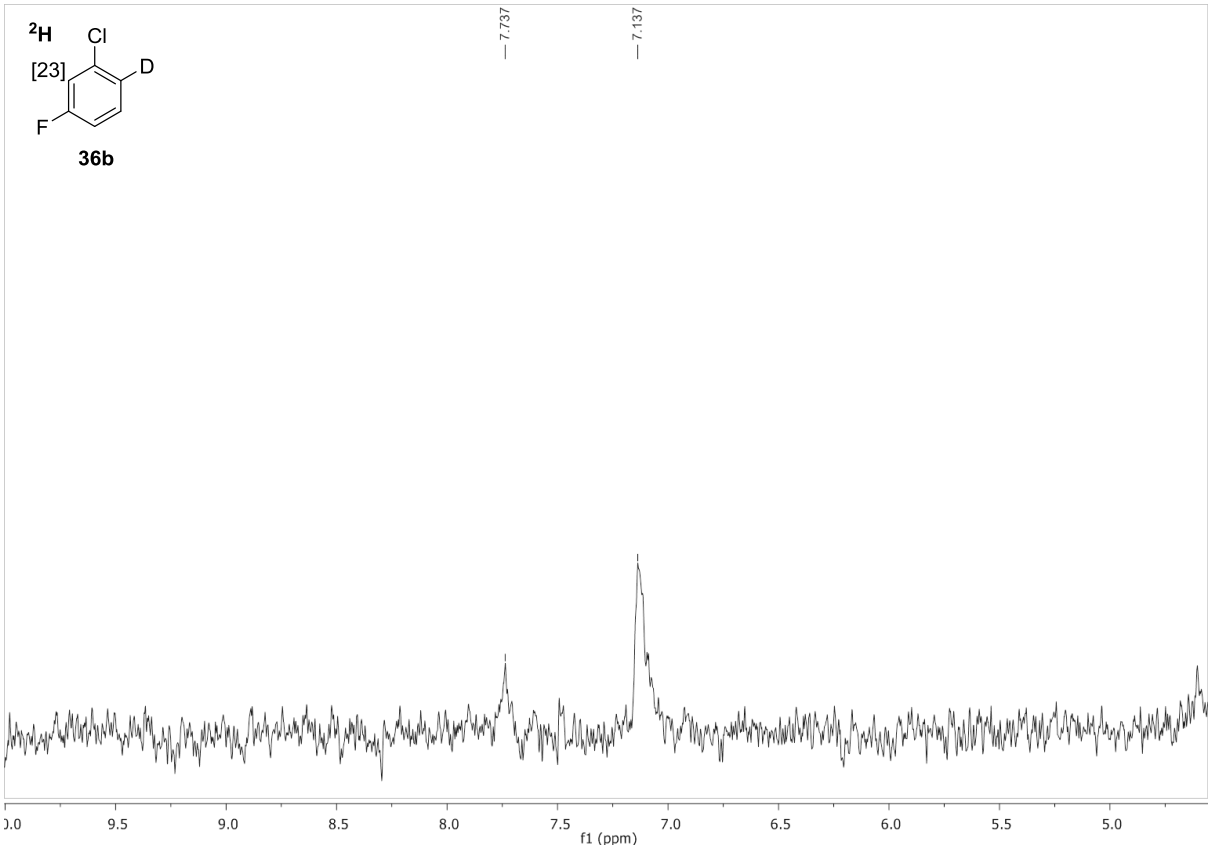




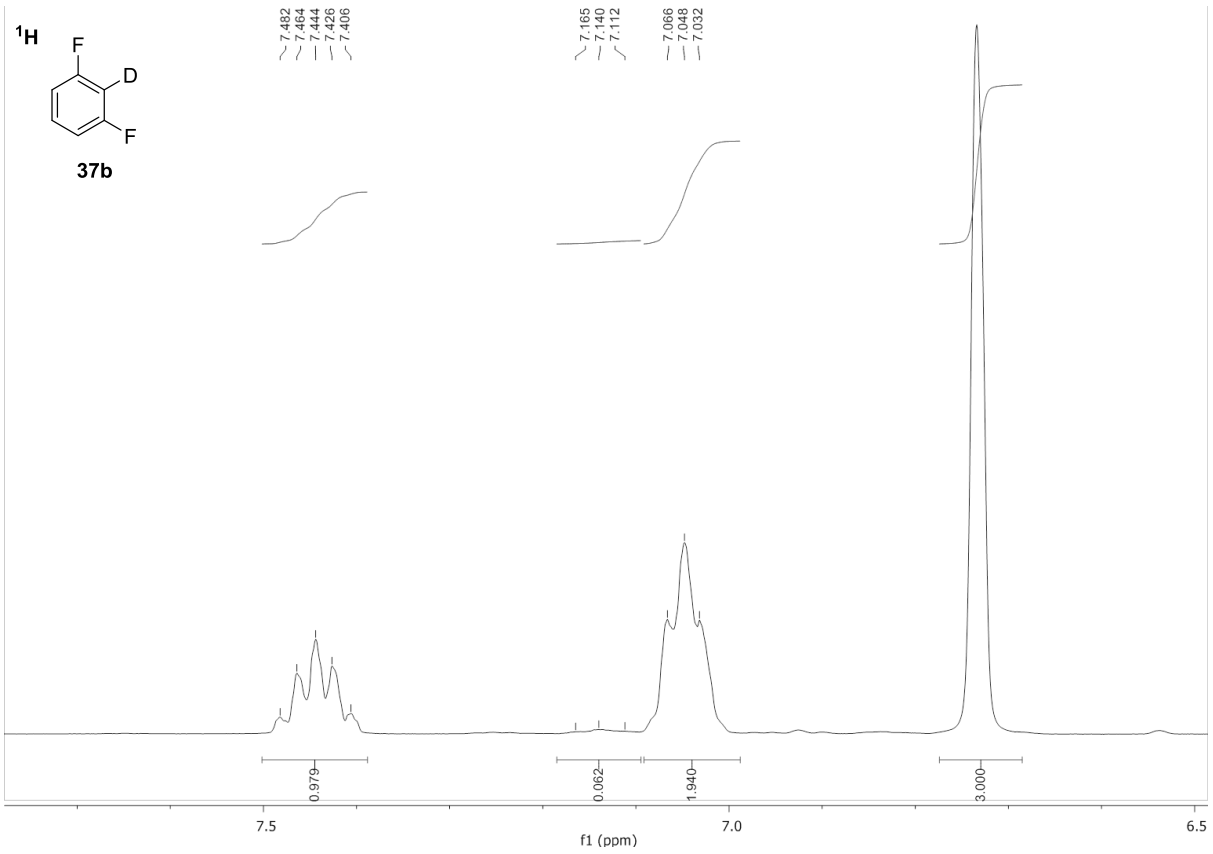


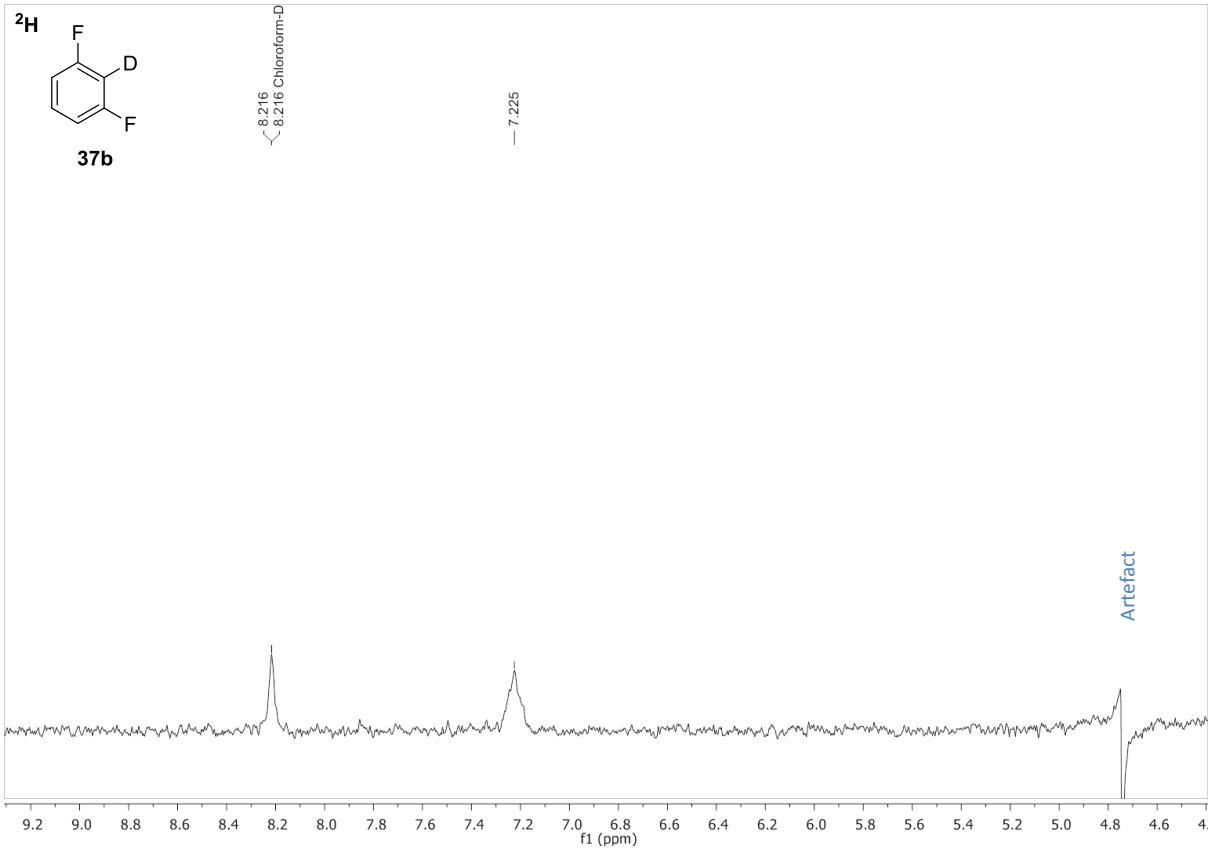
1-chloro-3-fluoro-6-deuterobenzene (36b)



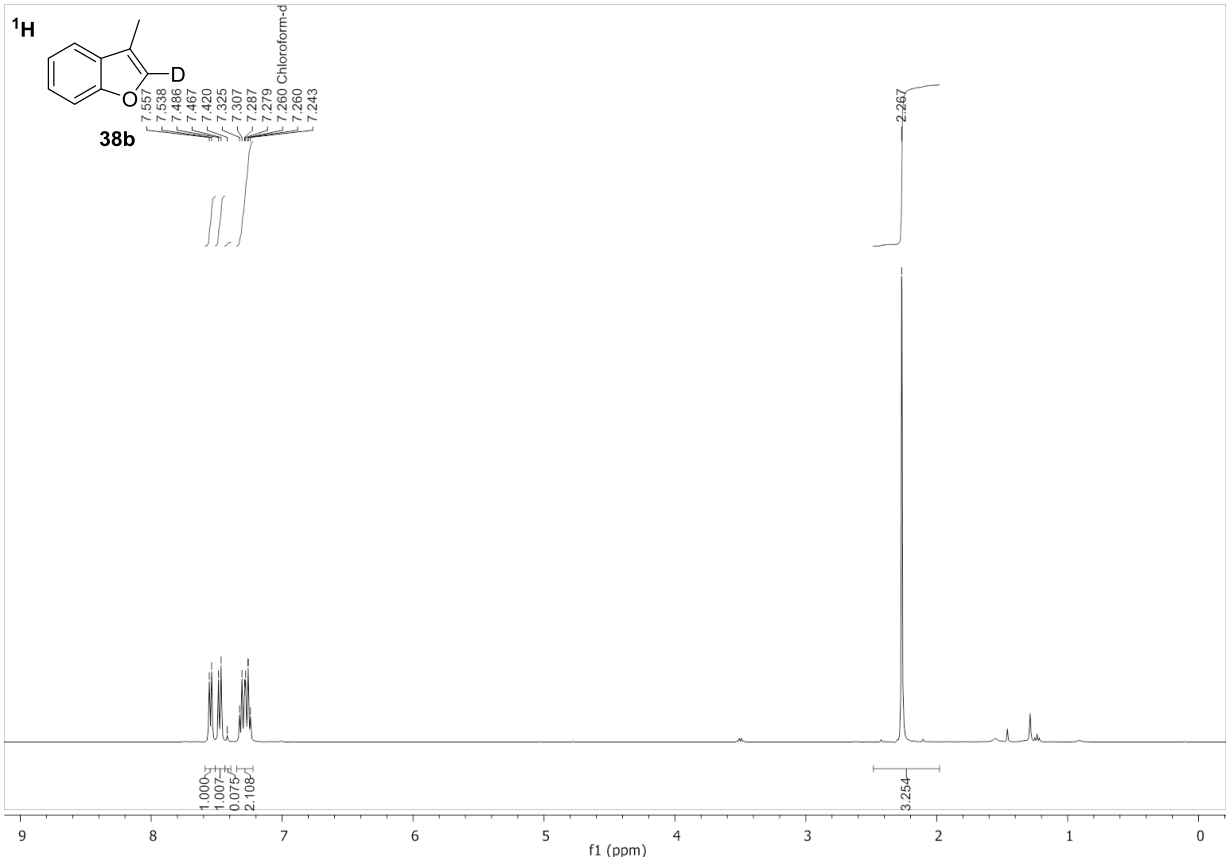


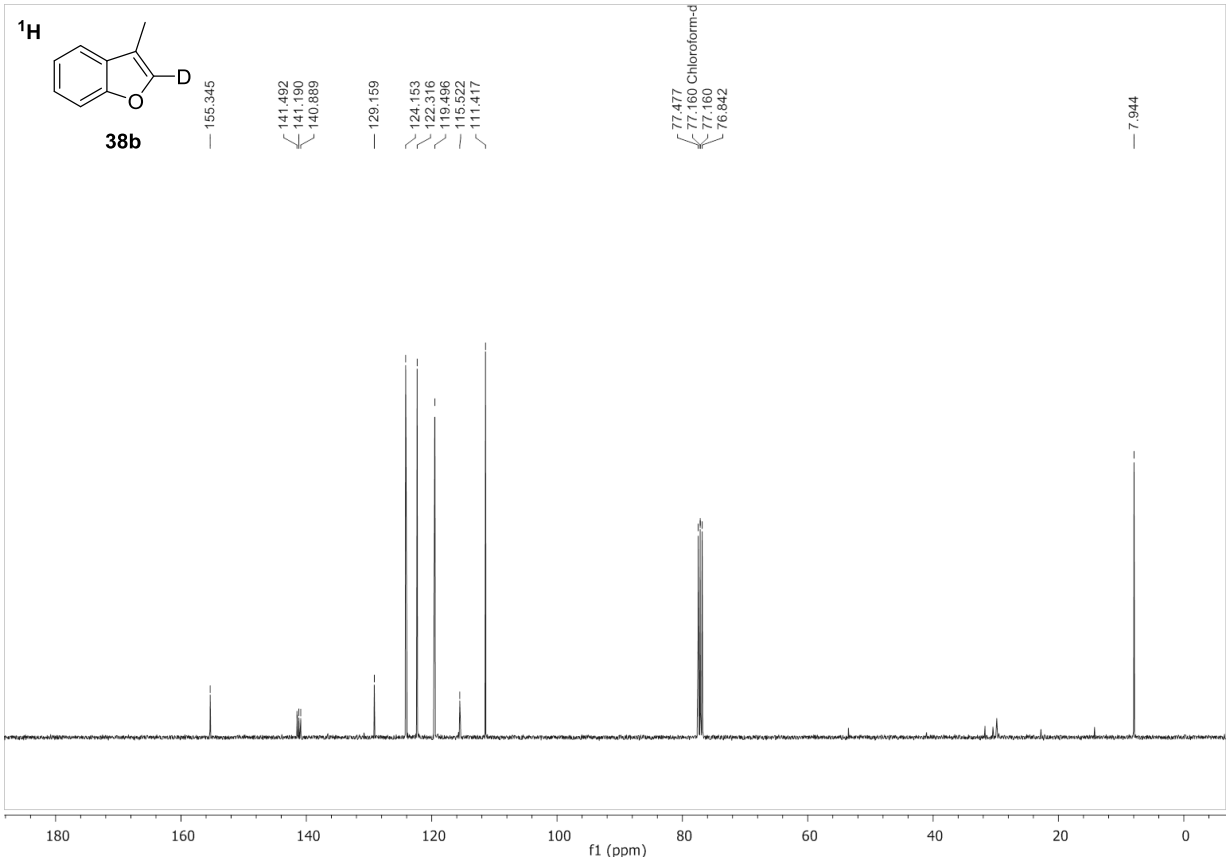
1,5-Difluoro-6-deuterobenzene (37b)

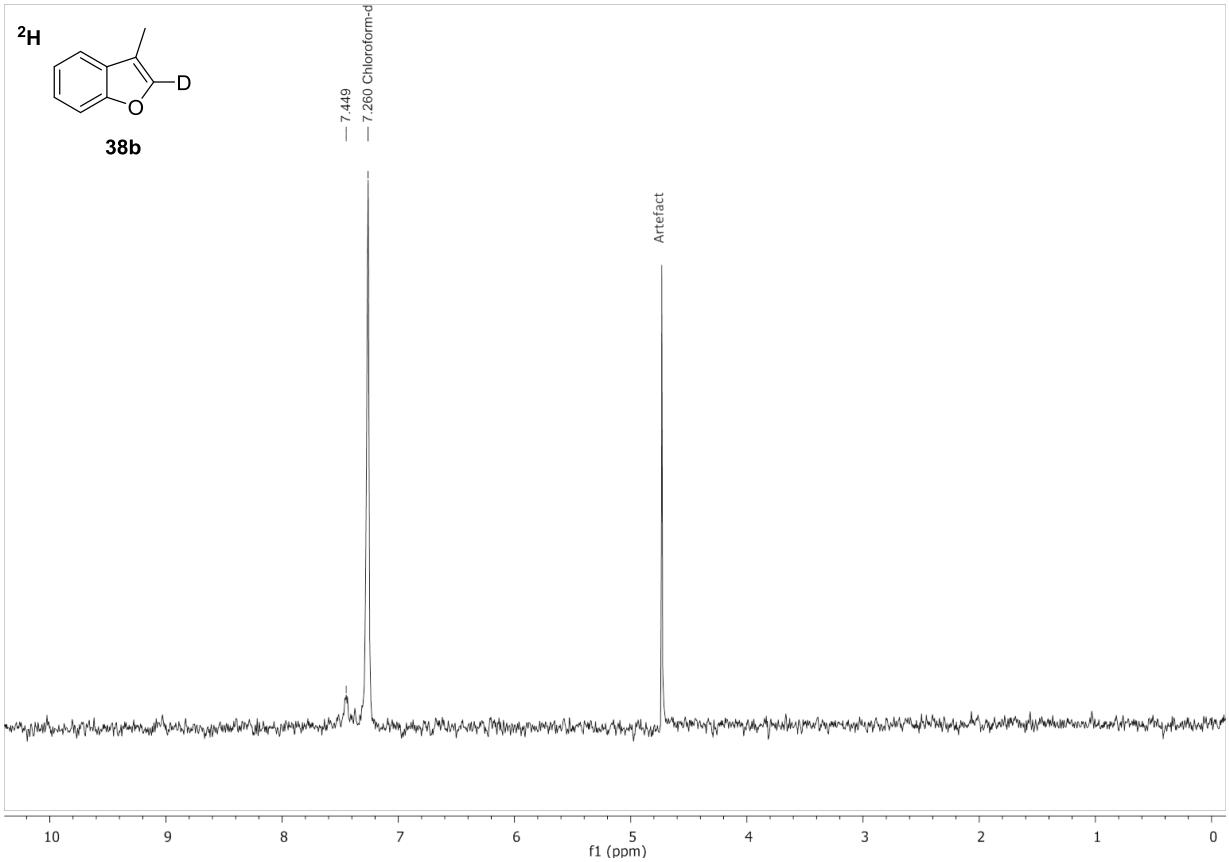




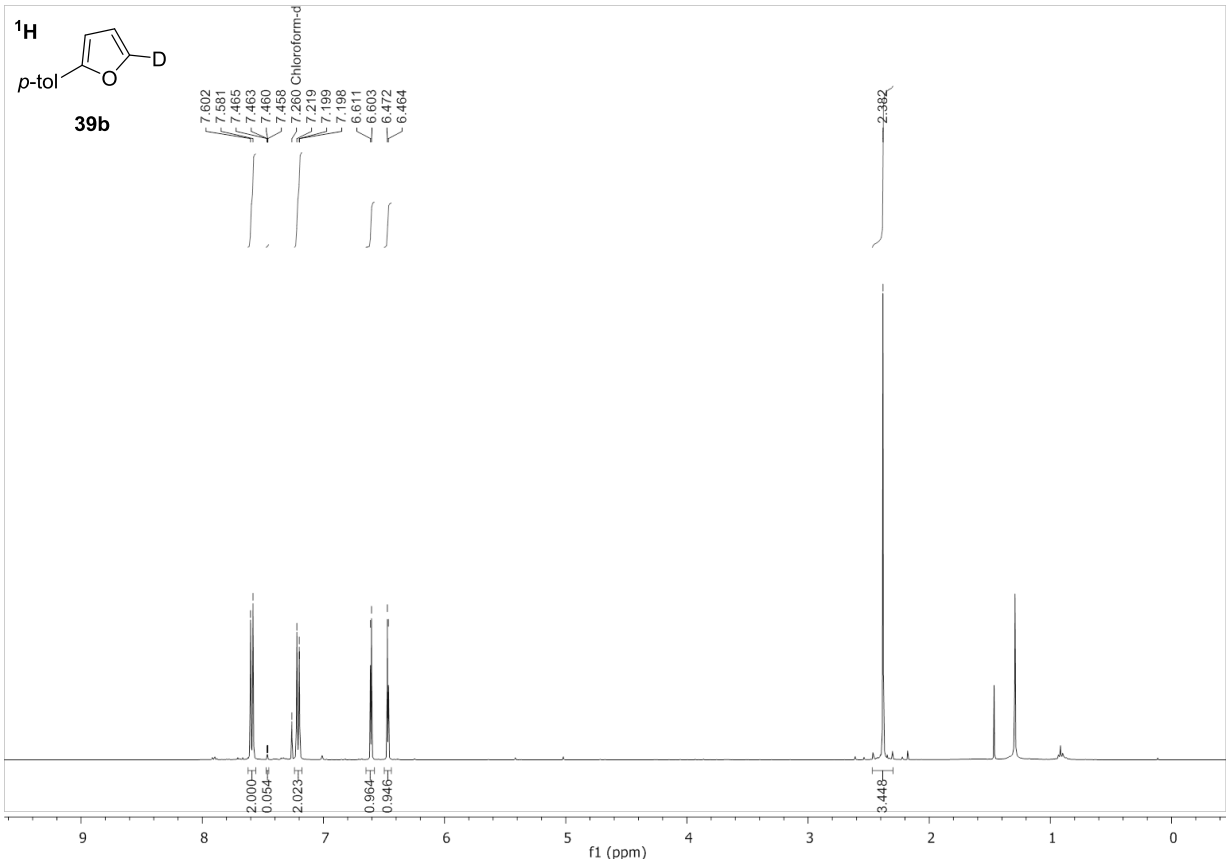
2-Deutero-3-methylbenzofuran (38b)

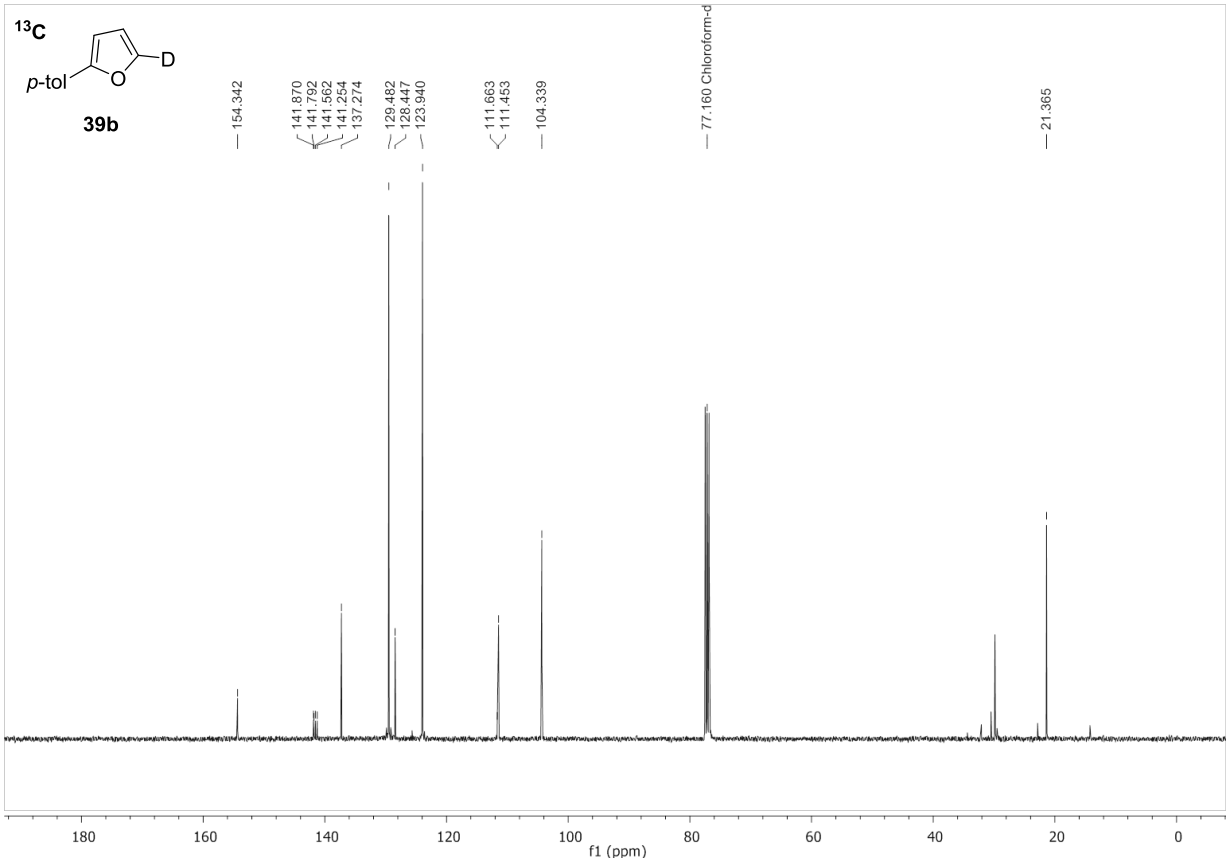


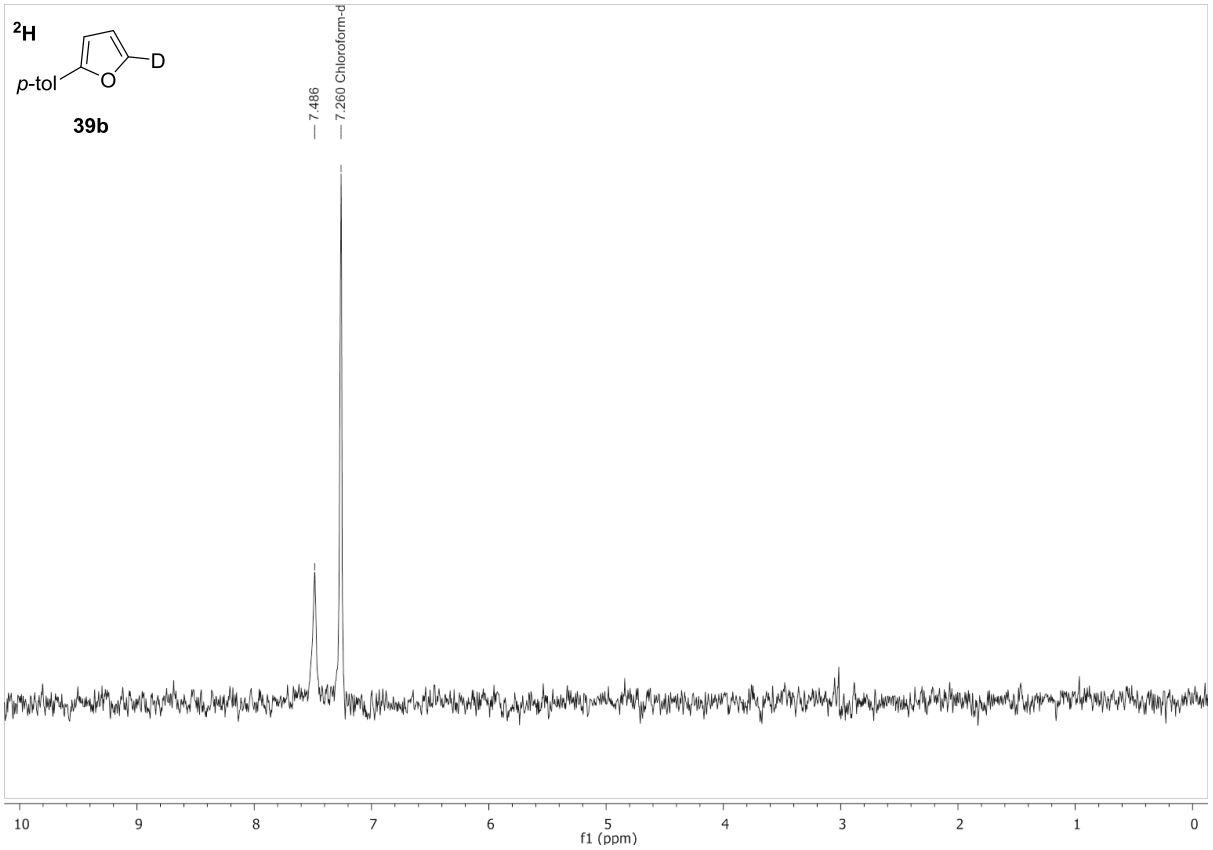

^{1}H
D
O
38b
155.345
141.492
141.190
140.889
129.159
124.153
122.316
119.496
115.522
111.417
77.477
77.160 Chloroform-d
77.160
76.842
7.944
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


^{2}H
D
O
38b
7.449
7.260 Chloroform-d
Artefact
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

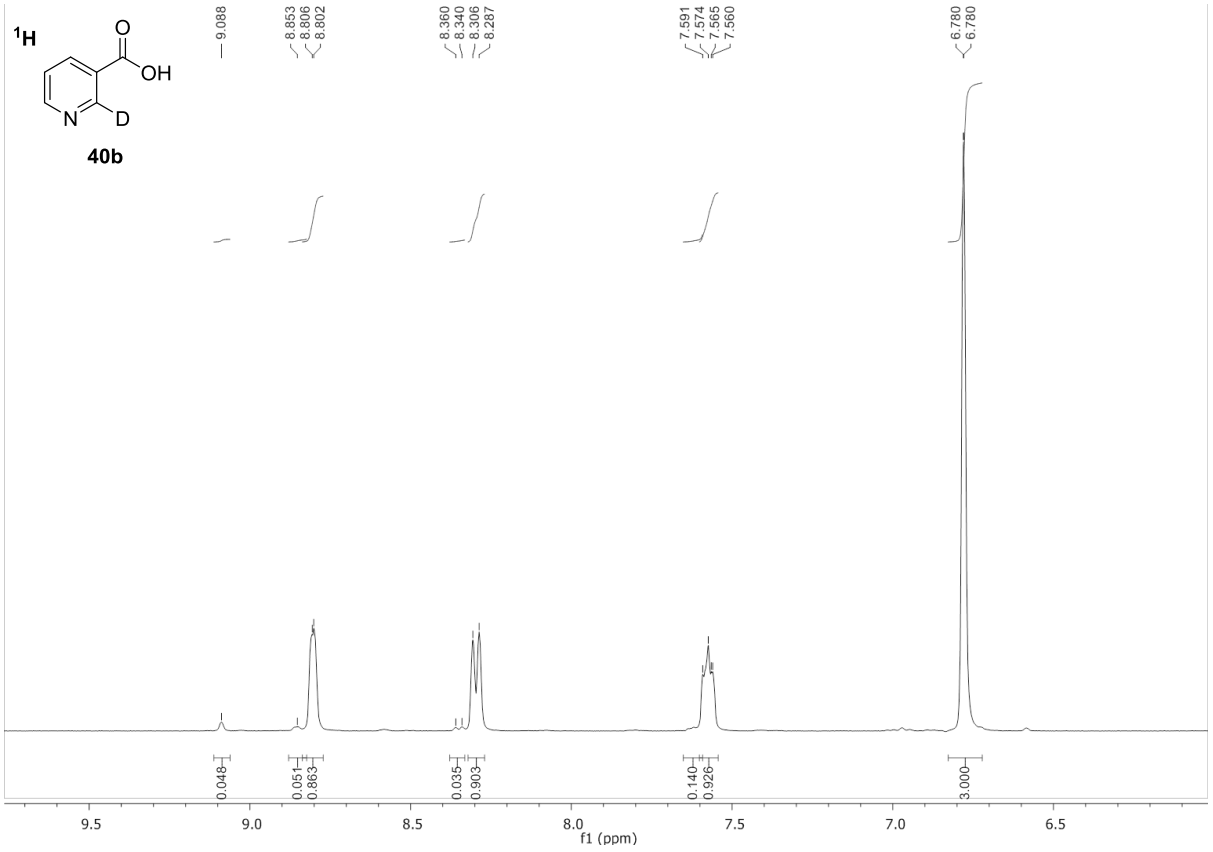
2-Deutero-5-(*p*-tolyl)furan (39b)

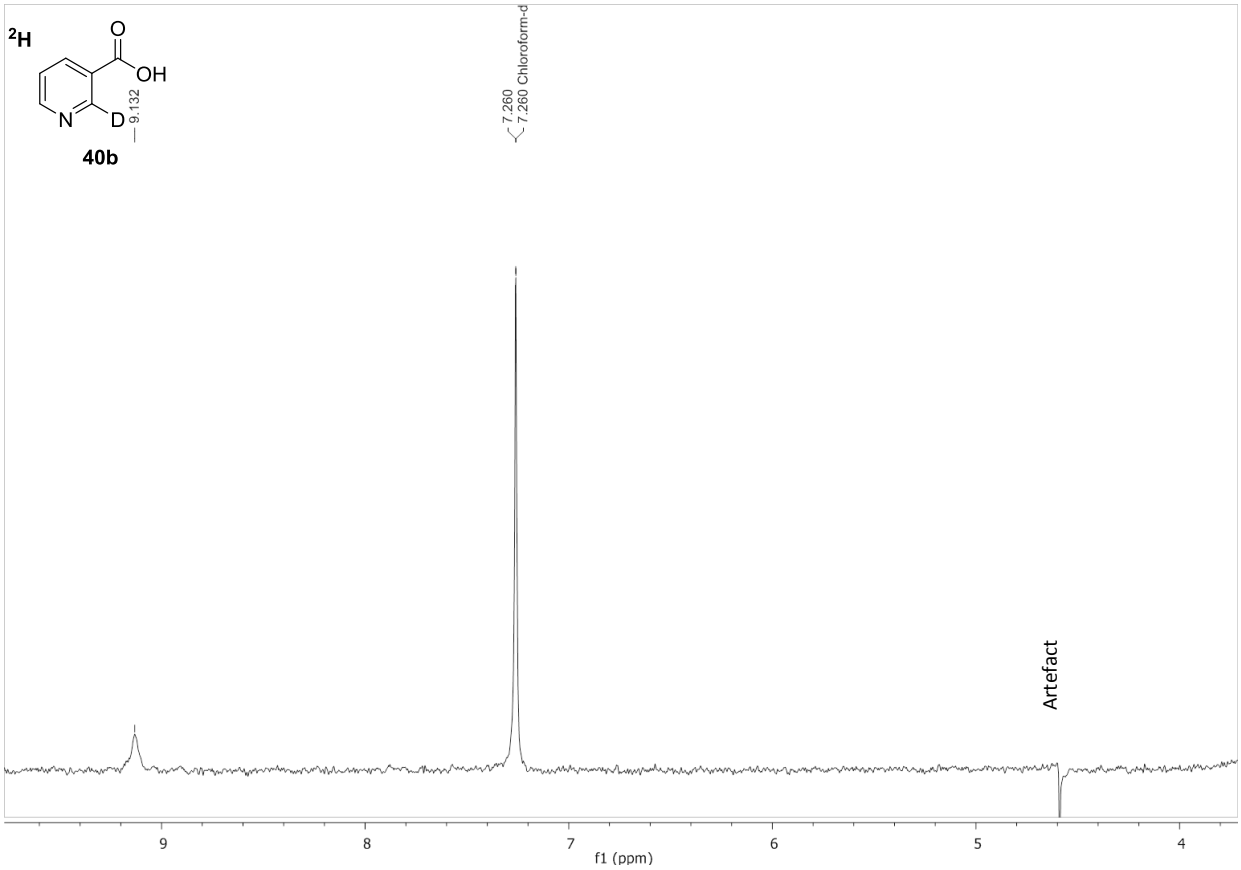




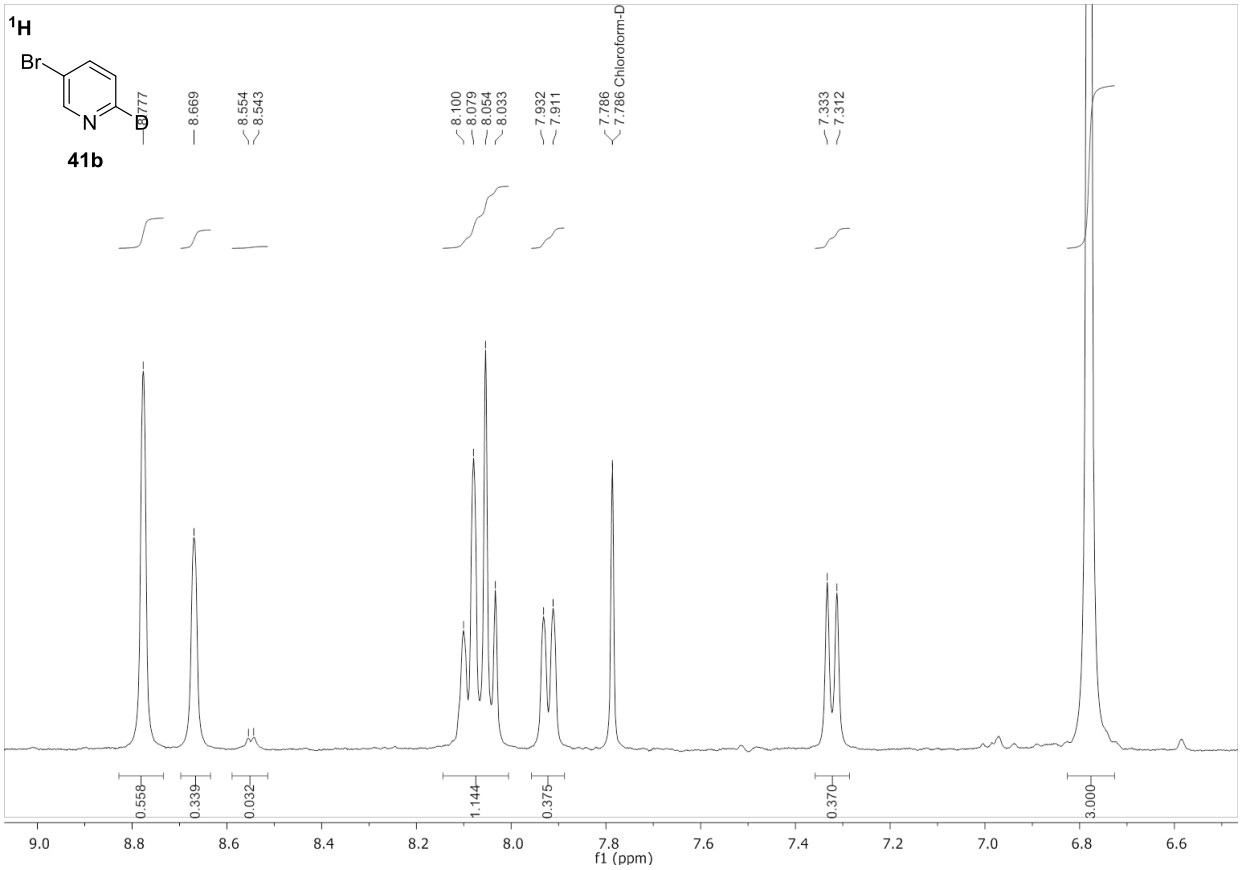


2-deutero-3-pyridinecarboxylic acid (40b)

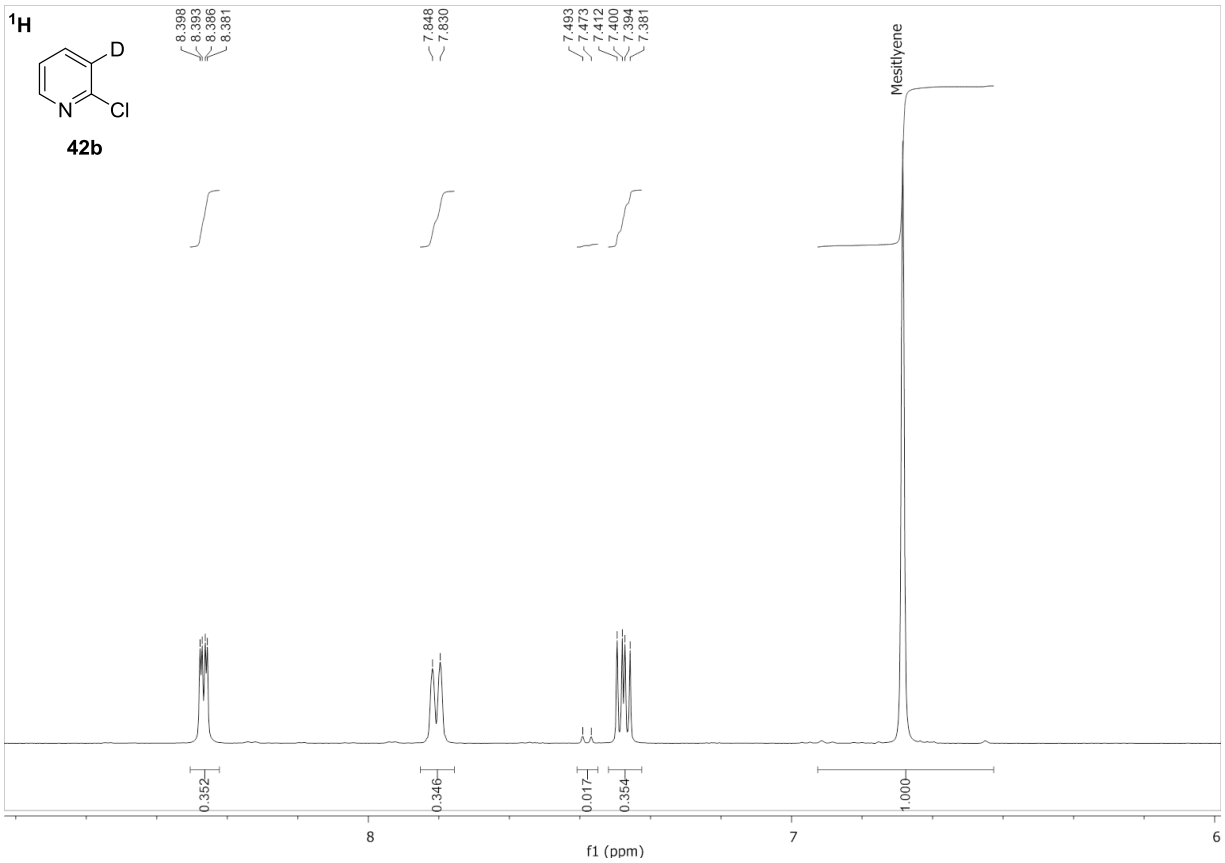


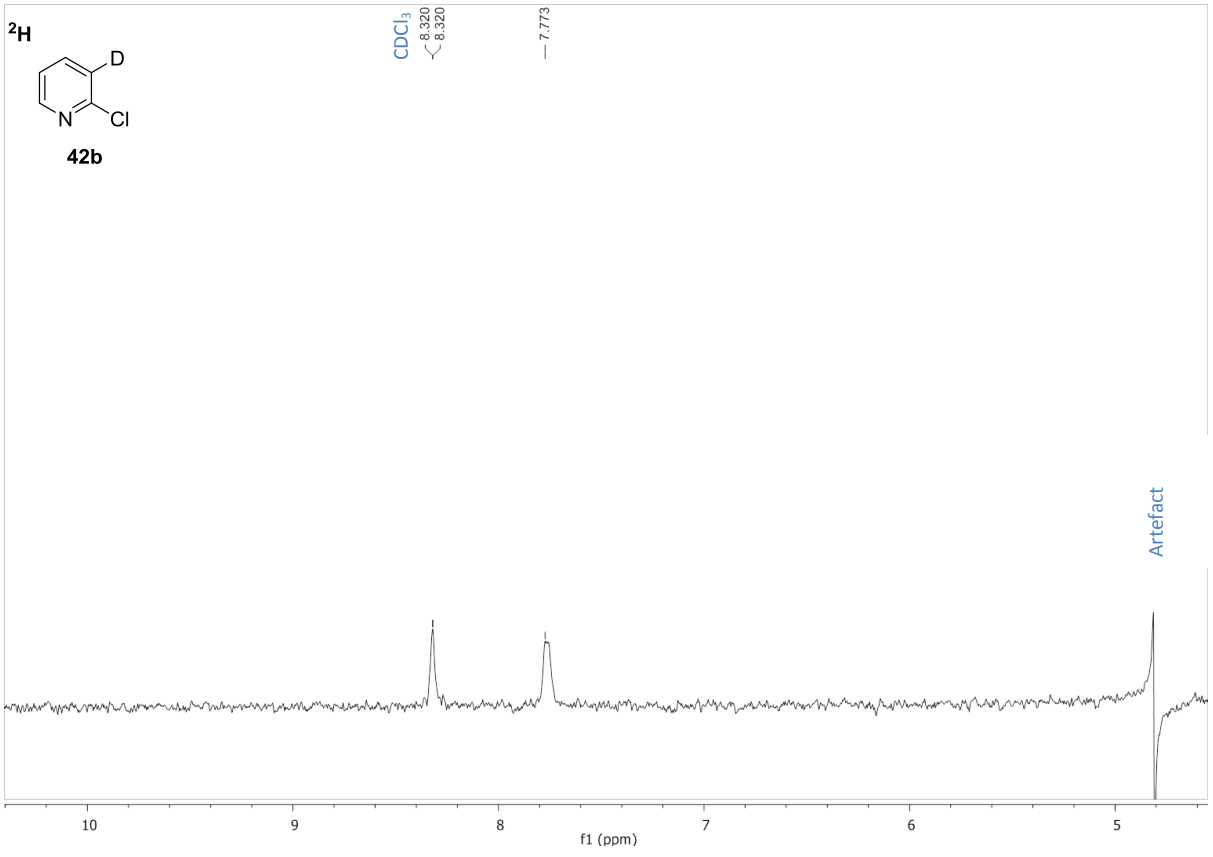


3-Bromo-6-deuteropyridine (41b)

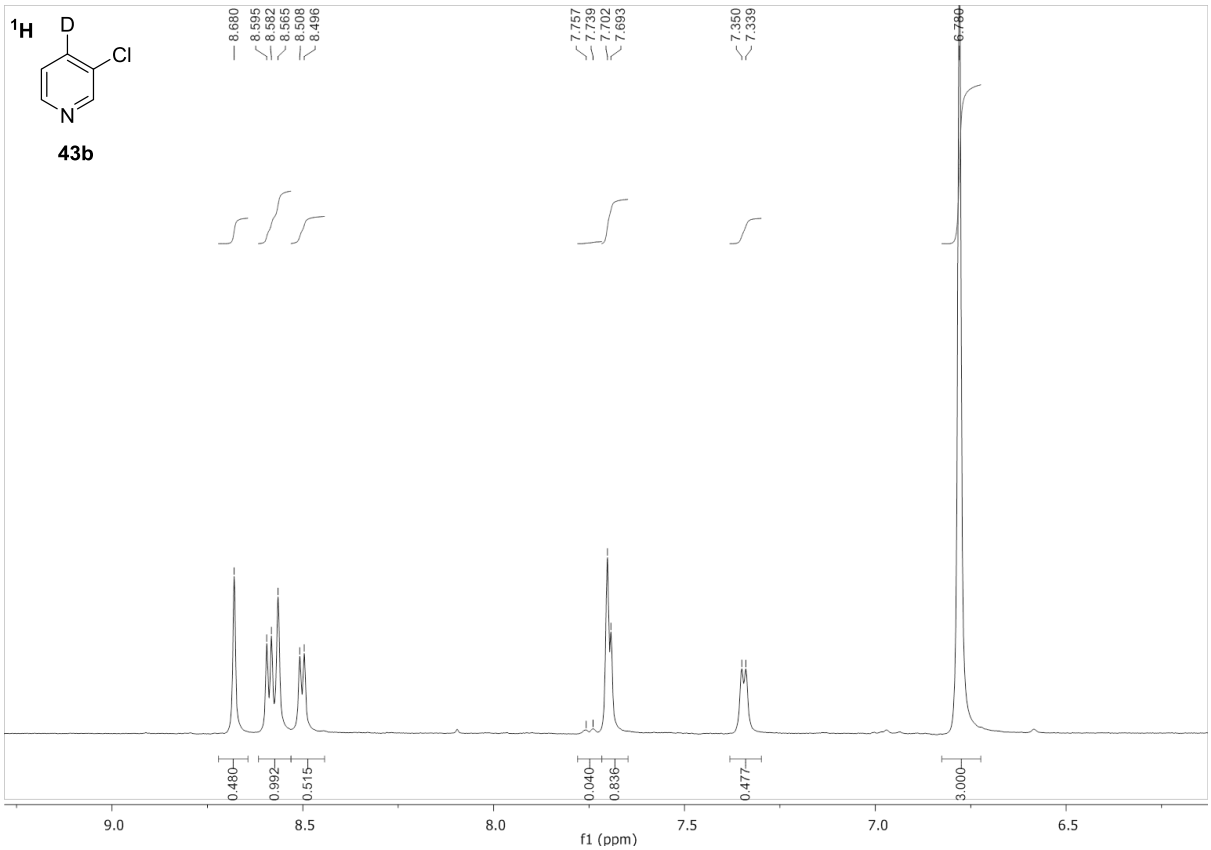


2-Chloro-3-deuteropyridine (42b)

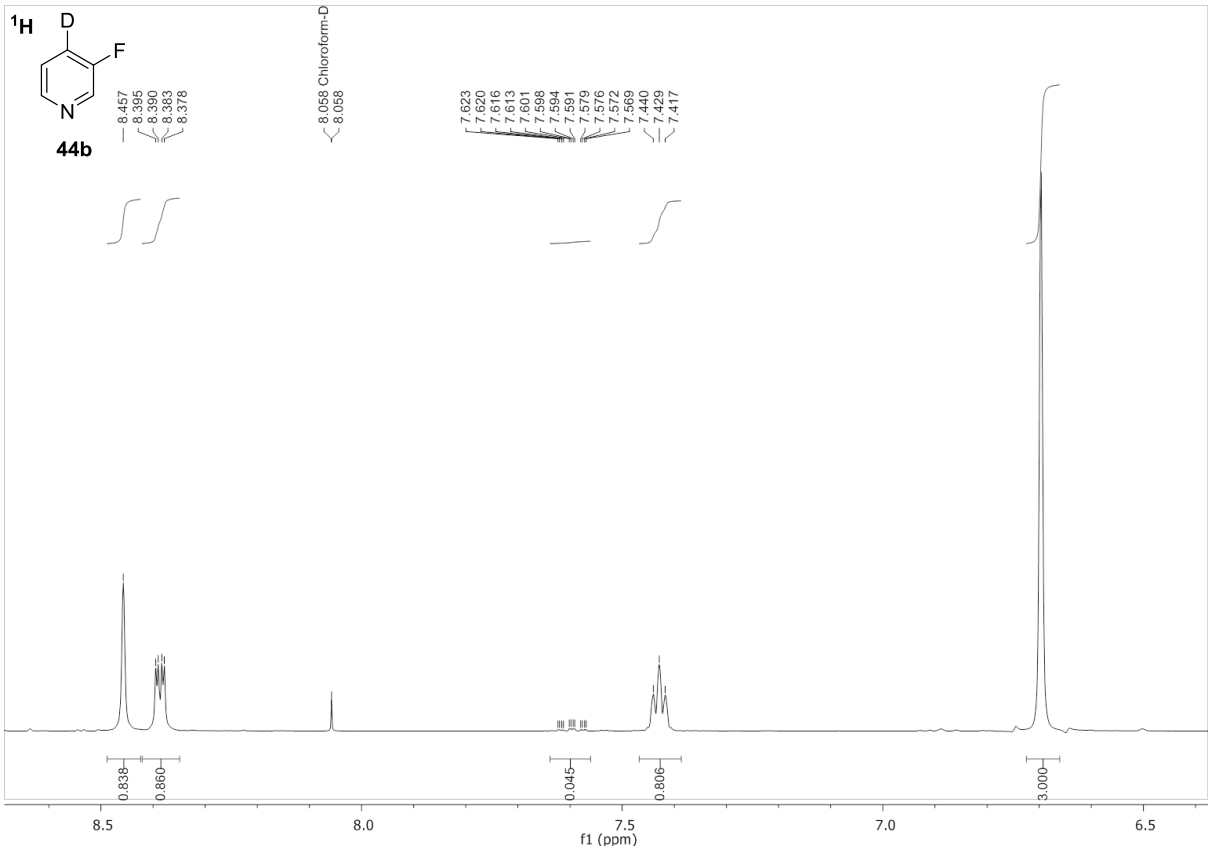


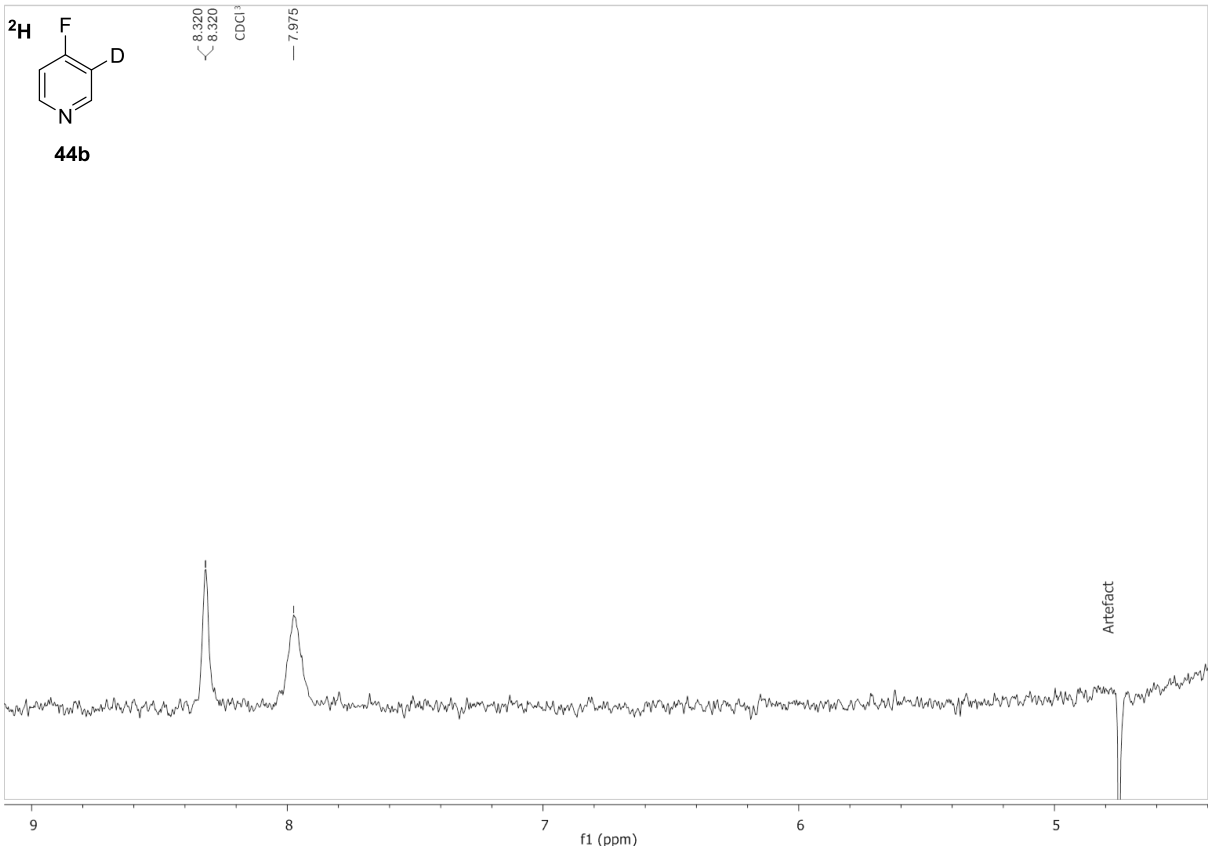


3-Chloro-4-deuteropyridine (43b)

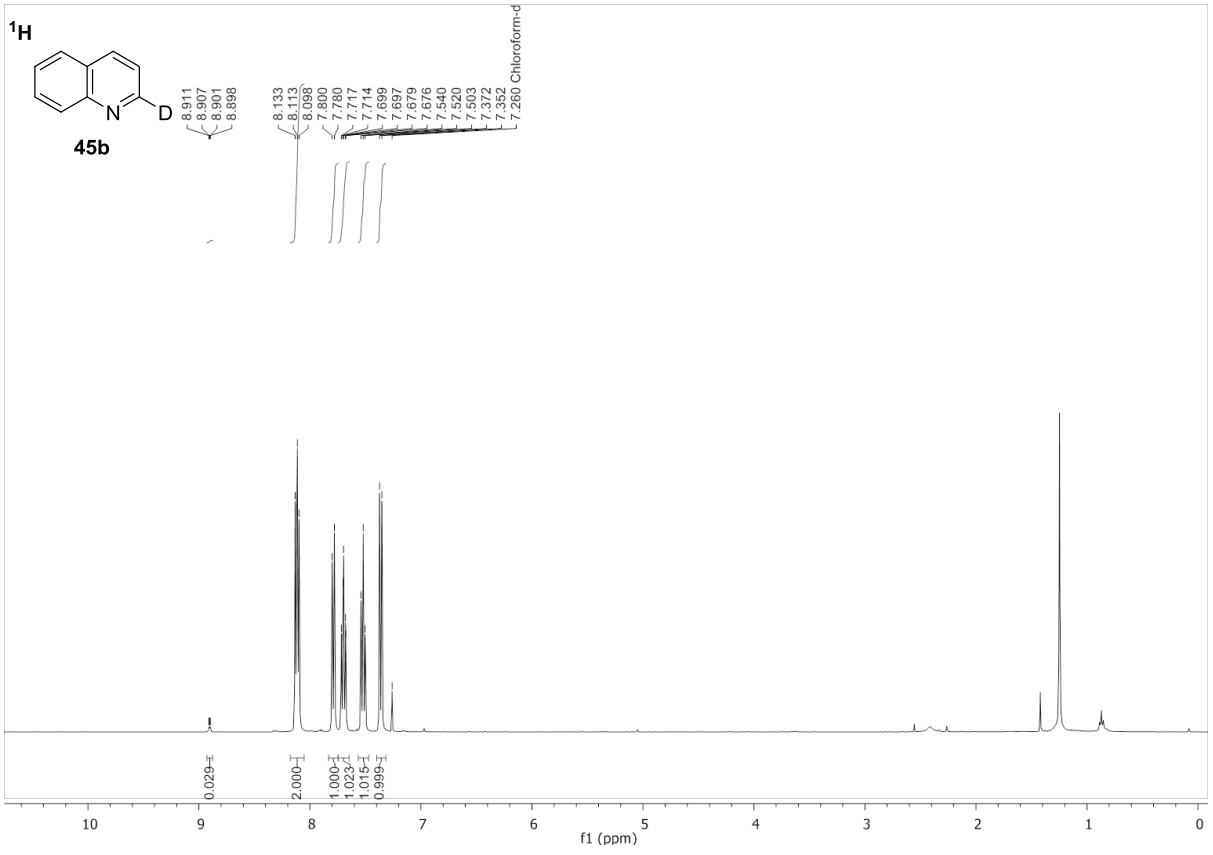


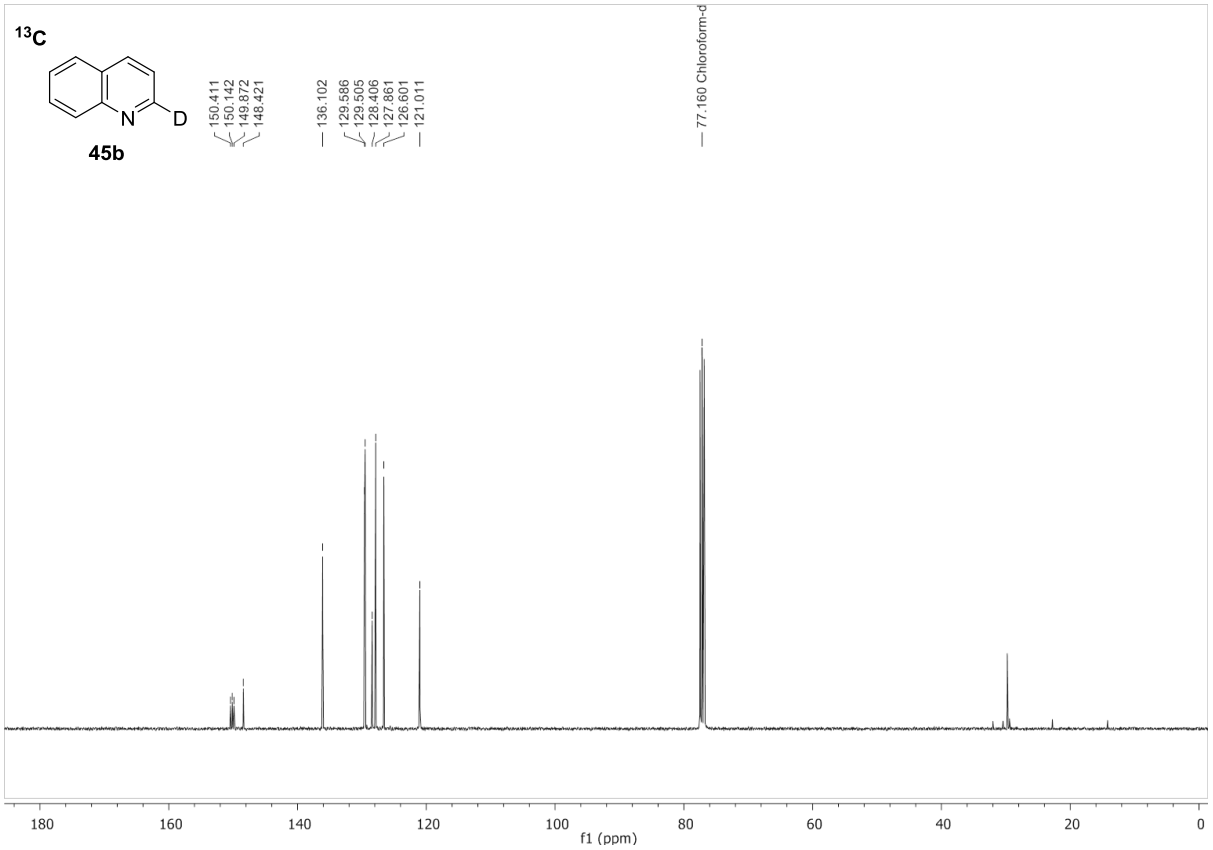
3-Fluoro-4-deuteropyridine (44b)

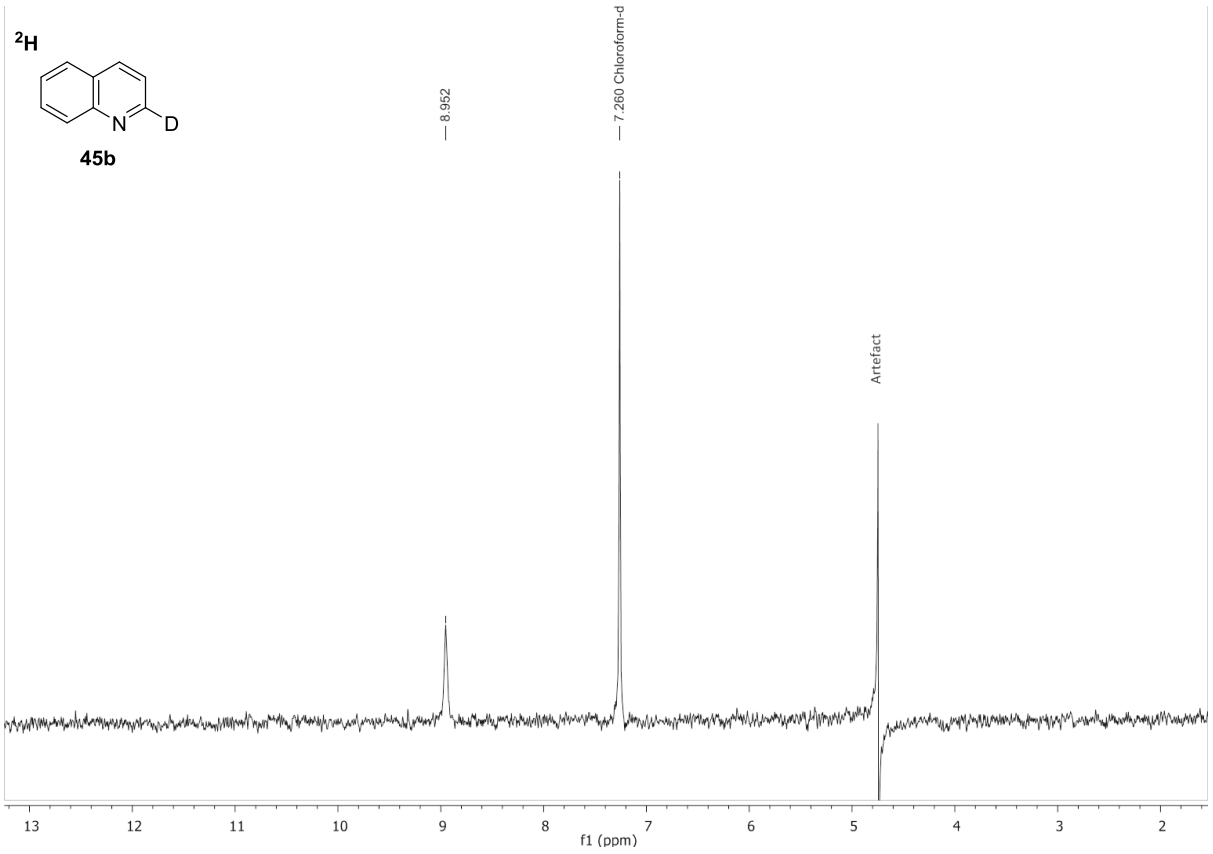




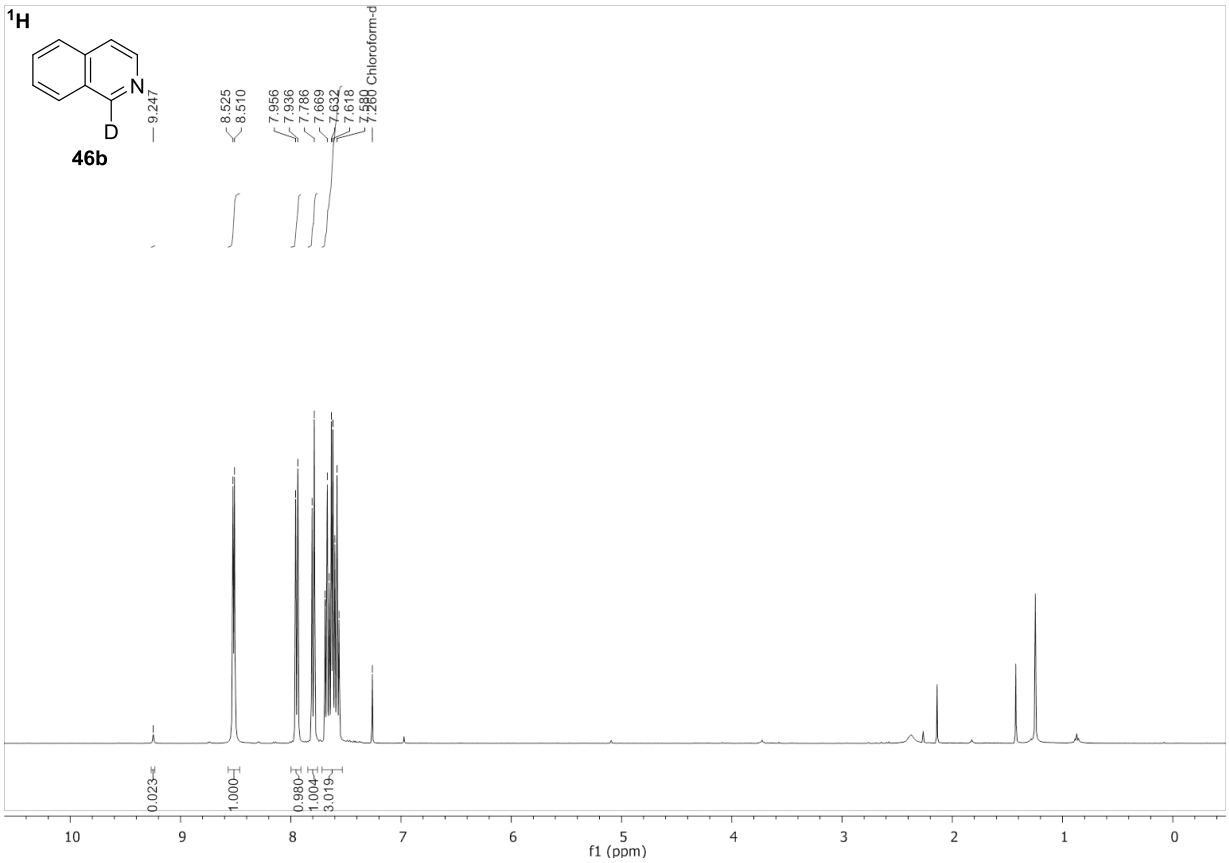
2-Deuteroquinoline (45b)

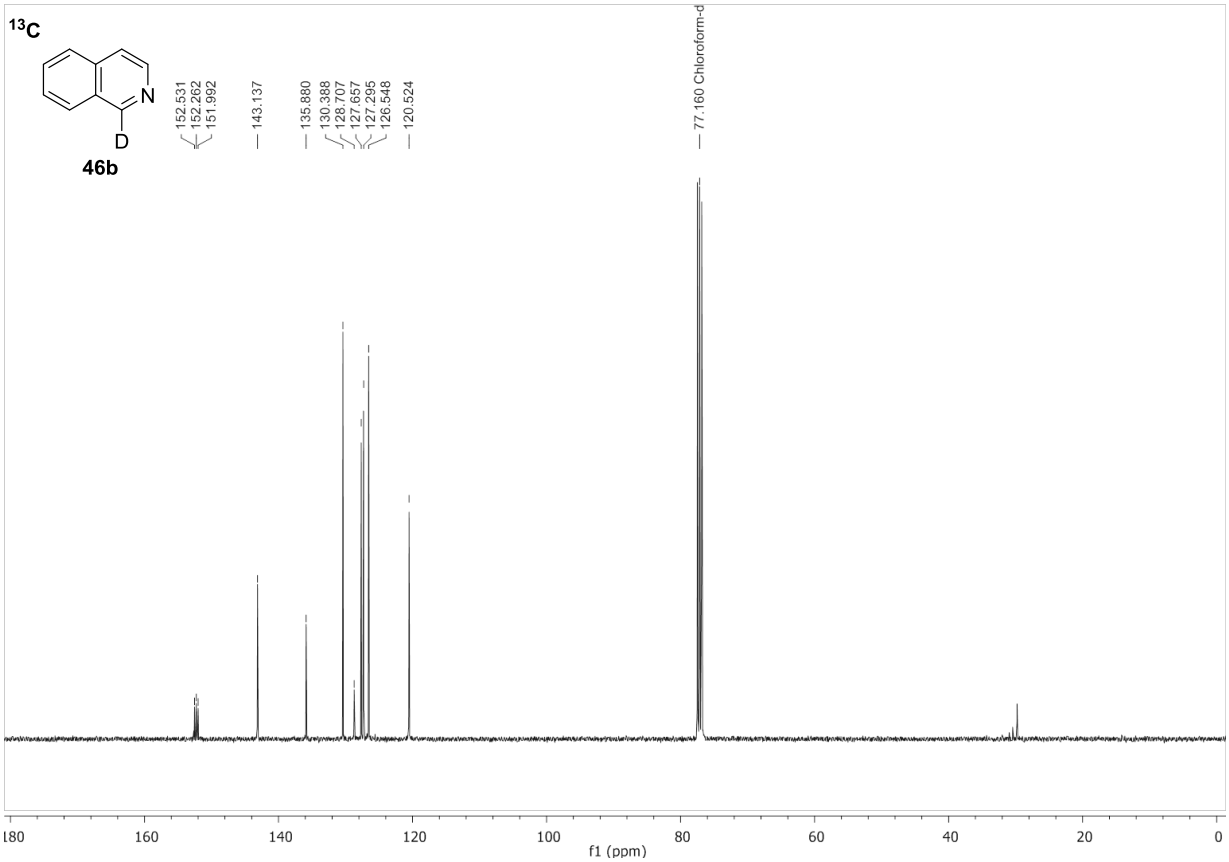


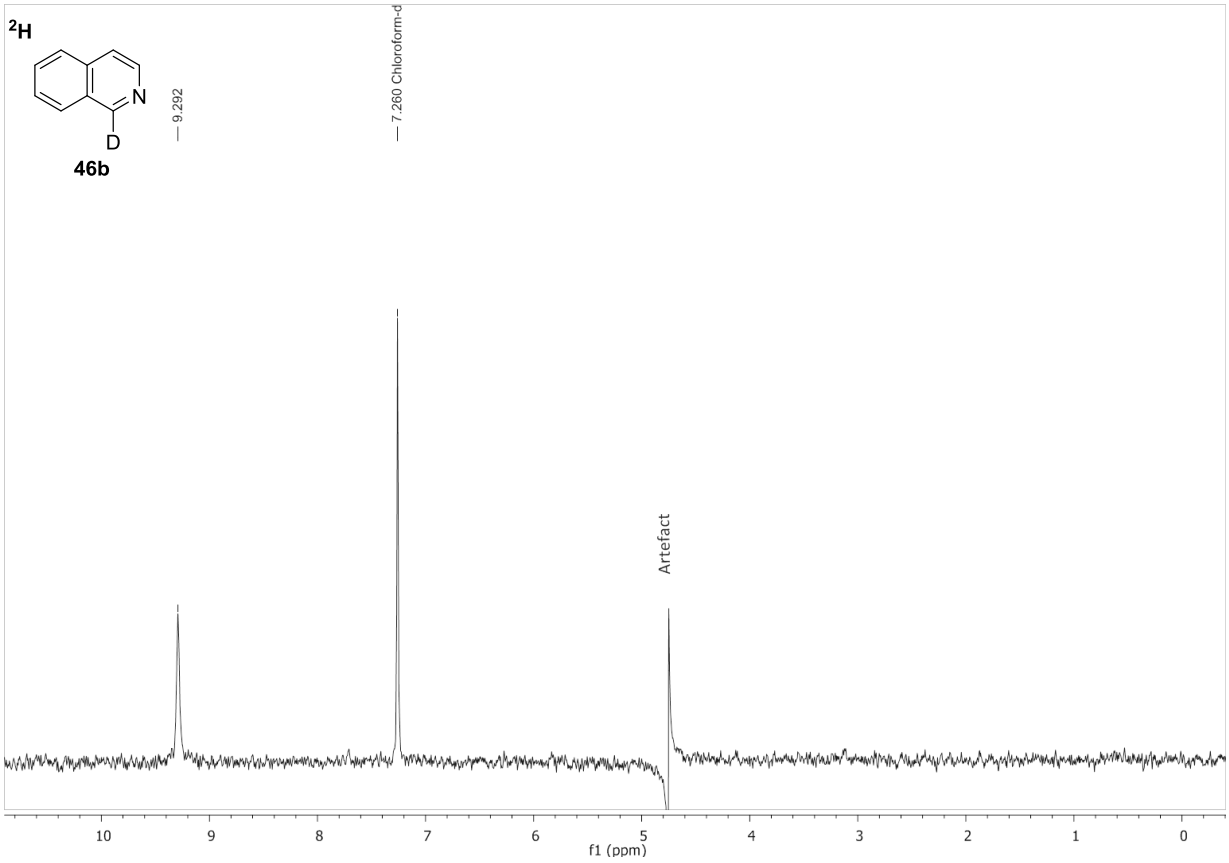

13C
N
D
45b
150.411
150.142
149.872
148.421
136.102
129.586
129.505
128.406
127.861
126.601
121.011
77.160 Chloroform-d
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


2H
N
D
45b
8.952
7.260 Chloroform-d
Artefact
13
12
11
10
9
8
7
6
5
4
3
2
f1 (ppm)

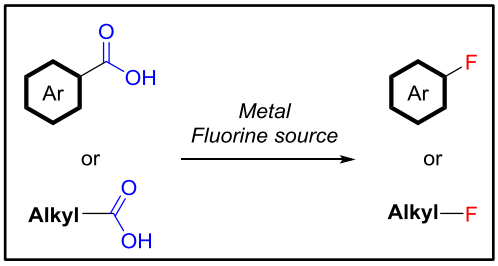
1-Deuteroisoquinoline (46b)






^{2}H
N
D
46b
9.292
7.260 Chloroform-d
Artefact
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

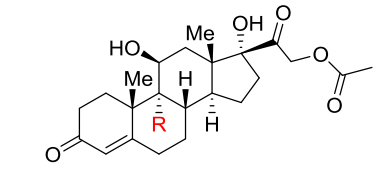
Chapter 3 – Development of a Transition Metal Catalysed Decarboxylative Fluorination Methodology



3.1. INTRODUCTION

Organofluorine compounds are of great importance to the agrochemical and pharmaceutical industries.[123] The incorporation of one or more fluorine atoms into a bioactive molecule can enhance a number of biological parameters, including lipophilicity, pK_a, conformational effects and molecular recognition.[123,124] The bioisoteric replacement of a hydrogen atom with fluorine results in minor steric alterations, however, the increased strength of the C–F bond can significantly retard the rate of metabolism and thus improve bioavailability. For example, the installation of a fluorine atom at the *para* position of a phenyl ring offers a dipole stabilisation and blocks the most likely point for oxidative metabolism to occur.[123d]

The first fluorine containing pharmaceutical (fludrocortisone) was discovered as a result of a systematic study of 9α-halogenated cortisone acetate derivatives. Fried and Sabo noticed that the anti-inflammatory activity of the halogenated steroids was lower for the larger halogens (I and Br) and increased by four-fold with the substitution of Cl for H, peaking at a ten-fold increase in activity for the fluorinated derivative (Scheme 61).[125] The de-acetylated variant, fludrocortisone, is on the World Health Organisation's (WHO) list of essential medicines.[126]



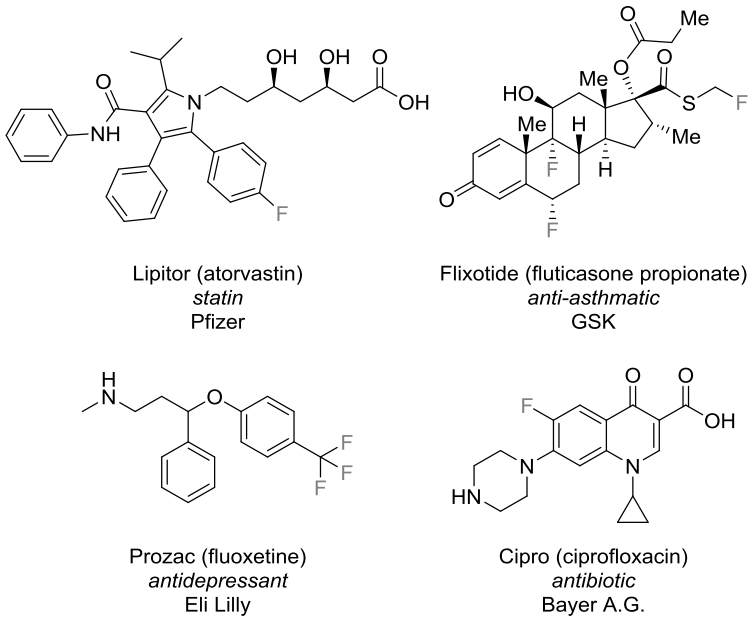
9α-halo-17α-hydroxycorticosterone acetate

R	Activity
H	1.0
I	0.10
Br	0.28
Cl	4.0
F	10.7

Scheme 61. Structure-activity relationship of 9α-halo-17α-hydroxycorticosterone acetate derivatives investigated by Fried and Sabo.[125a]

The impact of fluorine incorporation into bioactive molecules is so striking that between 1970 and 2014 the number of fluorine containing drugs on the market has expanded from 2% to approximately 25%.[127] Moreover, some of the most high revenue and well known 'blockbuster'

drugs are fluorinated, such as atorvastin (Lipitor) [peak sales of $13.6 bn (2006)] and Seretide/Advair Diskus (fluticasone propionate/salmeterol) [peak sales of $8.1 bn (2011)]. Furthermore, the World Health Organisation (WHO) list of essential medicines includes Prozac (fluoxetine) and Cipro (ciprofloxacin), which contain at least one fluorine atom (Scheme 62).[128]

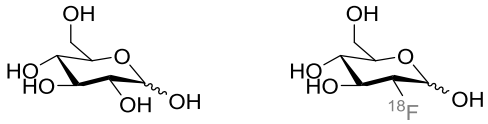


Scheme 62. Examples of fluorine containing bio-active molecules bearing aliphatic, perfluoroaliphatic, benzylic and aromatic C–F bonds.

The benefits of fluorination are not limited to small molecule agrochemicals and pharmaceuticals. The unique properties of fluorinated compounds have been exploited in other fields. Polytetrafluoroethylene (PTFE) was serendipitously discovered in 1938 and is marketed by DuPont as Teflon™, an invaluable non-stick coating for clothing and cookware. The strength of the carbon-fluorine bonds means that Teflon is very non-reactive and the high-electronegativity of the fluorine atoms results in a poly-fluorinated polymer which exhibits an extremely low coefficient of friction with other solids and is very hydrophobic.[129] Furthermore, the hydrophobicity and lipophobicity of perfluorinated compounds has found use in fluorous chemistry where fluorinated solvents form an immiscible 'fluorous phase' with water and organic solvents. This property can be exploited in many ways including catalyst recovery by fluorous tagging and improved green purification methods using perfluorinated solvents, which can be easily separated and recycled. [129,130]

Finally, the other main area in which fluorinated compounds are utilised is as tracers in the nuclear medical imaging technique, positron emission tomography (PET). The non-natural [^{18}F] isotope undergoes positron decay with a considerably longer half-life ($t_{½}$ = 110 min) compared to other commonly used radionuclides ([^{11}C] $t_{½\ 2}$ = 20 min, [^{13}N] $t_{½}$ = 10 min, [^{15}O] $t_{½}$ = 2 min), resulting

in increased incorporation into biological processes before decay occurs. In particular, the fluorinated glucose analogue 2-deoxy-2-[^{18}F]fluoro-D-glucose or [^{18}F]FDG is commonly used in cardiology and neurology but finds its most significant application in oncology due to the increased glucose uptake by cancer cells (Scheme 63). It is phosphorylated in the same manner as glucose, but due to the absence of a C2 hydroxy group, the [^{18}F]FDG cannot undergo glycolysis before it decays and remains trapped in the tissues under investigation. [^{18}F] PET scanning can be exceptionally valuable not only in the initial diagnosis of cancer, but also treatment planning, response to therapy and detection of recurrence of disease.[123a,131]



Scheme 63. Glucose and its fluorinated analogue [^{18}F]FDG commonly used as a tracer in PET imaging.

In spite of the plethora of uses for fluorinated compounds, there are a limited number of methods available for selective C–F bond construction that does not require harsh conditions or toxic reagents and can be carried out in short reaction times, a prerequisite for [^{18}F] incorporation. In recent years, the main focus in organofluorine chemistry has centred upon aryl C–F bond formation with a number of transition metal catalysed methodologies reported on functionalised and unfunctionalised arenes. Of late an increasing number of C(sp^3)–F methodologies have been reported and an overview of current routes to C(sp^2) and C(sp^3)–F bonds are discussed below.

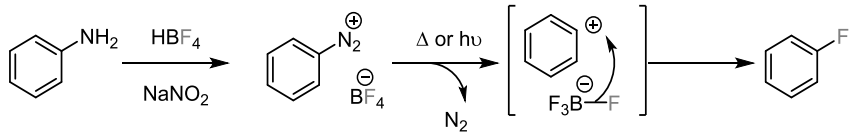
3.2. CURRENT METHODOLOGIES FOR ARYL FLUORIDE BOND FORMATION

3.2.1. Transition metal free nucleophilic fluorination

The main challenges in C–F bond formation arise from the fact that fluorine is the most oxidising and electronegative element, it has a small ionic radius and poor polarisability and thus the most abundant form of fluorine is as anionic fluoride. However, fluoride forms strong dipole-dipole interactions with hydrogen bond donors (e.g. alcohols, amines, amides etc) and has a large enthalpy of solvation; the consequence being that fluoride is weakly nucleophilic in the presence of protic species and forcing conditions can be required for reaction to occur.[129] Traditional routes to aromatic C–F bond formation using nucleophilic fluoride include the Balz-Schiemann and Halex (halogen exchange) reactions.

The Balz-Schiemann fluorodediazoniation reaction proceeds via diazotisation of an aniline in the presence of fluoride containing acid (e.g. HBF_4, HPF_6, $HSbF_6$) followed by either thermal or

photochemical decomposition of the resulting diazonium salt to afford the aryl fluoride (Scheme 64).[132,133] The mechanism is thought to proceed via S_N1 formation of a phenylium ion (on extrusion of N_2) which then reacts with nucleophilic fluoride from the counterion.[134] Phenyl cations are among the most unstable of all carbocations and thus the highly forcing conditions required to achieve C–F formation using this method indicates the huge energetic cost, despite the entropic benefit on forming N_2.

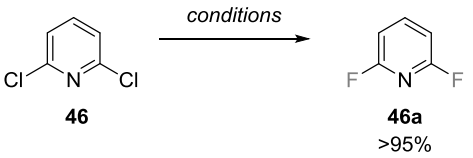


Scheme 64. The Balz-Schiemann reaction involves formation of aryl C–F bonds on loss of N_2.[132]

Diazotisation with $NOBF_4$ can be employed to improve yields and broaden reaction scope, however high temperatures (110-170 ^oC) are still required for the pyrolysis step. In 2001 Laali *et al.* reported an improved fluorodediazoniation protocol using reusable ionic liquid solvents which permit reactions at lower temperature (30-120 ^oC) in excellent yields. Moreover, the protocol could be utilised for the formation of aryl- trifluroroacetates, tosylates and triflates by changing the counterion of the ionic liquid.[135] Subsequently, Kirk *et al.* reported a photochemical version for the formation of fluorinated heterocycles in ionic liquids, the reaction proceeds at room temperature or 0 ^oC. However the yields were mediocre and in some cases the reaction was carried out over several days to improve yield.[136]

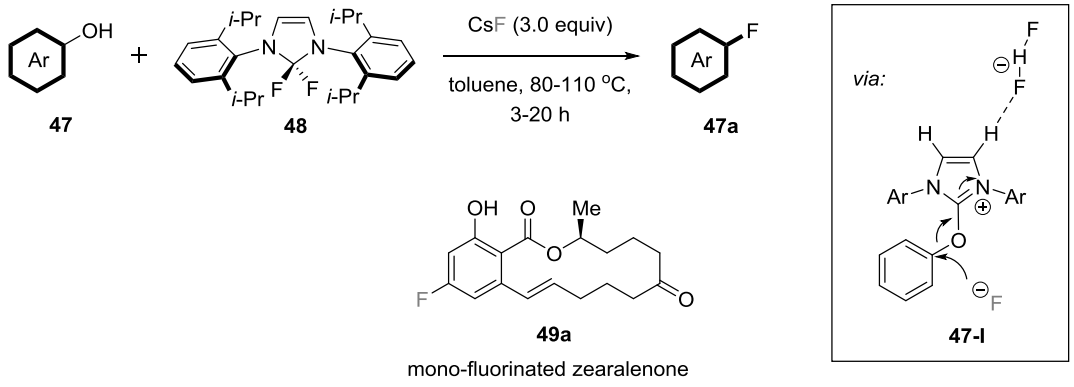
The Halex process is a method commonly employed in industry for the commercial synthesis of fluorinated building blocks. Electron-deficient aryl halides undergo halogen exchange with inexpensive inorganic fluorides, such as KF.[137] The best yields are achieved with (hetero)aromatic chlorides, however high temperatures (~190 °C) and significant reaction times (≥ 9 h) are required for halogen exchange. This is due to the difficulty in obtaining stringently anhydrous fluoride sources and the concomitant reduction in fluoride nucleophilicity in the presence of moisture (Scheme 65, conditions A).[133,138]

In 2006, DiMagno *et al.* reported a protocol for the preparation of anhydrous TBAF from hexafluorobenzene and tetra-n-butylammonium cyanide.[139] Using anhydrous TBAF as the fluoride source, the Halex process can be significantly optimised with reaction taking place rapidly at ambient temperature with quantitative yields (Scheme 65, conditions B). As shown in Scheme 65, the fluorination of dichloropyridine (**46**) can be greatly improved using this methodology compared to the standard approach. A variety of different arenes and heteroarenes can be fluorinated using this protocol however at least 2 electron-withdrawing groups or heteroatoms are required on the aromatic ring for reaction to occur.



Scheme 5. Comparing the Halex of 2,6-dichloropyridine (**46**) using traditional (A) and optimised conditions (B).[133,138,139]

Recently the Ritter group reported an aromatic deoxyfluorination of phenols (**47**) using a novel nucleophilic fluorinating agent Phenofluor (**48**) (Scheme 66).[140] The reaction is operationally simple, and unlike the Halex reaction, it tolerates a wide variety of arenes including those with electron-donating and electron-withdrawing groups. This methodology was employed in the late stage fluorination of estrone, 6-hydroxy-*O*-acetyl-quinine and remarkably zearalenone which underwent mono-fluorination to give **49a**, with the second phenolic oxygen remaining untouched due to participation in intramolecular hydrogen bonding with the adjacent ester carbonyl (Scheme 66).[140]



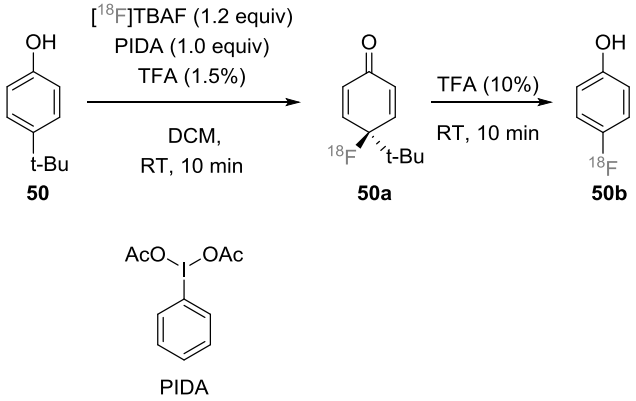
Scheme 66. Deoxyfluorination of phenols using the novel fluorinating reagent Phenofluor **3** reported by Ritter *et al.*[140]

The reaction proceeds via nucleophilic attack of the phenol on **48**; double displacement of the fluorides gives an activated phenolic ether with a bifluoride counterion **47-I**, the structure of which was confirmed by X-ray crystallography. Other commercially available deoxyfluorinating agents such as Xtalfluor-E, Xtalfluor-M, DAST and Deoxyfluor gave no trace of conversion; similar to **48**, all of these reagents work by covalent linkage to the alcohol thus forming an improved nucleofuge which is subsequently displaced by fluoride. It is hypothesised that Phenofluor has superior activity due to the bifluoride anion which is a strong hydrogen bond acceptor[141] and improves the leaving group ability of the uronium moiety and/or in apolar solvents the resulting tight ion pair holds the fluoride closer to the *ipso* carbon. The formation of the urea carbonyl is also a strong thermodynamic driving force to favour displacement; however imidazolium salts which lack the ability to form similar

hydrogen-bonded complexes with the bifluoride anion were unable to afford detectable amounts of product.[140]

So far the approaches discussed towards aryl C–F bond formation use functional group interconversions in the presence of nucleophilic fluorine and inherently afford excellent selectivity due to the nature of the transformations. Despite the advances in this field, these approaches suffer limitations including modest yields and excessive reaction times (~7 days for the Halex reaction) and the requirement for electron-deficient arenes. For example, using the optimised Balz-Schiemann conditions, 2,6-dichloropyridine undergoes rapid di-fluorination at ambient temperature whereas mono-chloropyridines are completely unreactive.[139] The deoxyfluorination protocol reported by the Ritter group offers an excellent option for metal-free nucleophilic fluorination of aromatics regardless of the electronic properties of the substrate. However the required fluoride source (Phenofluor **48**) involves a 2 step synthesis and rapidly hydrolyses if stored in a wet atmosphere;[140] this reagent is now commercially available but is extremely expensive considering it is required in stoichiometric amounts.[vii]

Recently Gouverneur and co-workers reported the metal-free oxidative fluorination of phenols using nucleophilic fluoride sources (Scheme 67).[142] Their work builds upon previous reports of the fluorination of phenols in the presence of hypervalent-iodine oxidants such as PIDA.[143] This approach reverses the reactivity of the phenol allowing it to undergo nucleophilic attack at C4 which is hypothesised to occur via generation of a hypovalent phenyloxenium ion by two-electron oxidation with PIDA.



Scheme 67. Metal free oxidative fluorination of phenols with $[^{18}F]F^-$ reported by Gouverneur *et al.*[142]

The reaction was initially optimised by Gouverneur *et al.* utilising pyridine-HF as the fluoride source and 4-*tert*-butylphenol substrates (**50**). In acidic conditions, the generation then

[vii] Sigma Aldrich; Phenofluor (SFL00001, CAS = 1314657-40-3) = £158 for 250 mg ≡ £270/mmol

rearomatisation of fluoro-cyclohexadieneones (**50a**) occurs on elimination of *iso*-butene, rapidly generating the product (**50b**). This approach was then translated to the rapid [^{18}F]-fluorination of a variety of 4-fluorophenols, which are an important structural submotif in PET radiochemichemistry, in good radiochemical yields (RCY).[142]

3.2.2. Transition metal free electrophilic fluorination

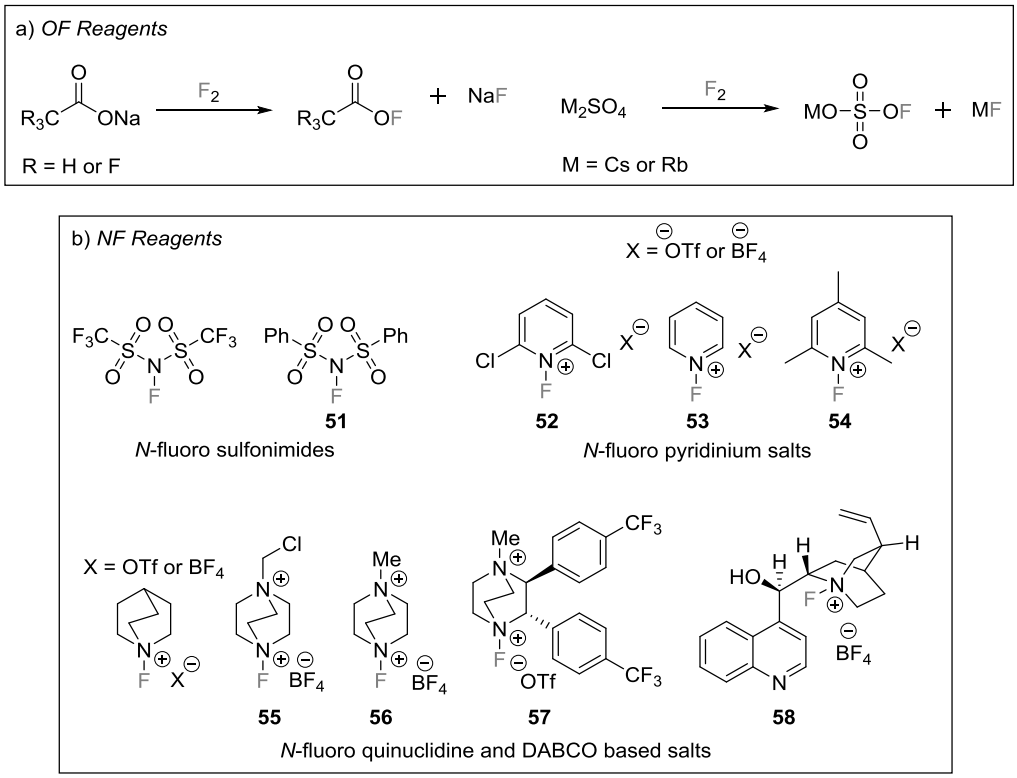
Elemental fluorine was successfully isolated by Henry Moissan in 1886.[144] The sustained effort and danger associated with this task earned Moissan the Nobel Prize in Chemistry in 1906; with the accompanying quotation:

"...in recognition of the great services rendered by him in his investigation and isolation of the element fluorine...The whole world has admired the great experimental skill with which you have studied that savage beast among the elements."[145]

The low F–F bond energy (153 kJ mol^{-1}) resulting from the strong repulsion of the lone pair electrons on the fluorine atoms, in conjunction with the strength of subsequent bonds formed with other elements make fluorine gas a powerful oxidiser which reacts with almost any organic compound usually in an exothermic and often explosive manner.[146] In the 1960s, fluorine was first 'tamed' by diluting F_2 in inert carrier gases such as N_2 or Ar; these mixtures are commercially available and provide more control and selectivity however specialist equipment and handling is still required.[147]

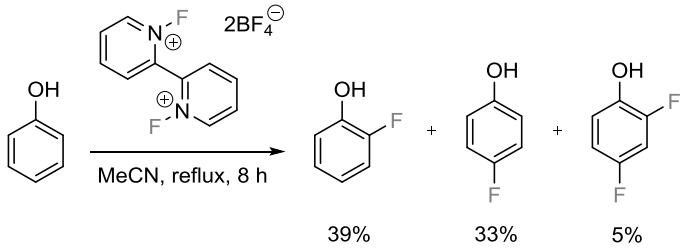
High reactivity, lack of selectivity, toxicity and risk of free radical initiated runaway reactions are all properties that make working with elemental fluorine highly challenging. Nonetheless, since it was first isolated by Moissan in 1886, it remained the only reagent for 80 years that could successfully facilitate electrophilic fluorinations. F_2 can be used to prepare less reactive O–F fluorinating agents such as acyl hypofluorites or fluoroxysulfates (Scheme 68), however these compounds are still highly reactive, toxic and potentially explosive. Furthermore, they are not commercially available and have to be freshly prepared from F_2 prior to use. Xenon difluoride is a powerful electrophilic fluorinating reagent with the first reported isolations in 1962.[148] XeF_2 is a white crystalline solid produced from a mixture of Xe and F_2 with heat, irradiation or electrical discharge. Although commercially available, it is highly oxidising and relatively unstable, decomposing on exposure to light and moisture vapour and explosively in the presence of acetates. In the past 20 years a major breakthrough in electrophilic fluorination chemistry has been engendered with the availability of stable N–F electrophilic fluorinating reagents. This class of fluorinating agents was first reported in the early 1980s.[149] Since then a wide variety of these

crystalline, moisture stable reagents for fluoronium transfer have been synthesised and a number are commercially available (Scheme 68b, **51**-**56**); furthermore, the inexpensive nature and ease of handling of these reagents means that they are widely used in research. Cahard and Shibata first reported the synthesis of chiral fluorinating reagents based on cinchona alkaloids (e.g. **58**) which can be rapidly obtained by transfer fluorination with Selectfluor **55.**[150] Recently, Gouverneur and Sandford reported a new class of DABCO based chiral fluorinating agents (e.g. **57**); however F_2 gas is required for the synthesis (Scheme 68b).[151]



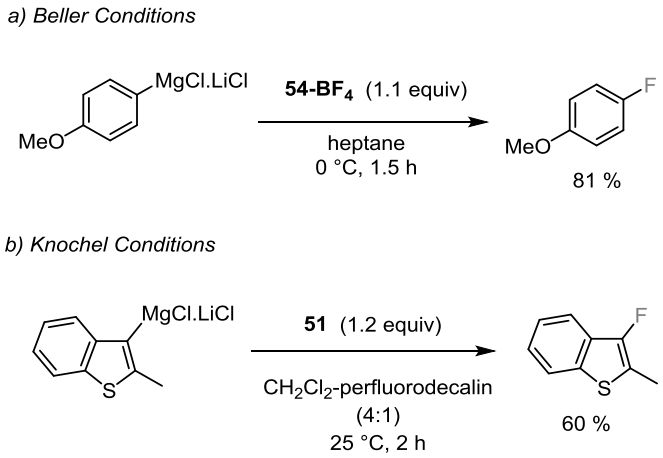
Scheme 68. Examples of reagents derived from F_2 a) hypofluorite and fluorosulfate OF reagents; b) sulfonamide, pyridinium, quinuclidine and DABCO based NF reagents.

Aromatic fluorination (in the absence of transition metal catalysts or without prior deprotonation or metallation) can be largely unselective with elemental fluorine, XeF_2, OF and NF reagents and is dependent on the inherent reactivity of the substrate; for example mesomeric activators such as OMe, OH, NHAc direct reaction at the *ortho* and *para* sites and thus regioselectivity can be an issue unless other sites can be blocked prior to reaction (as exemplified in Scheme 69).[133,152] Regioselective fluorination can be achieved with the use of common organometallic reagents such as Grignards and organolithiums; however reaction yields are highly substrate dependent.[133,149c,153]



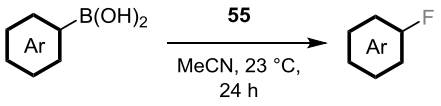
Scheme 69. Unselective fluorination of phenol with an electrophilic N—F fluorinating reagent.[133,152]

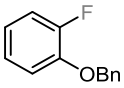
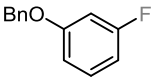
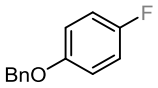
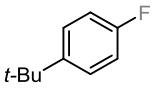
In 2010, Beller and Knochel independently reported improved conditions for the formation of aryl fluorides from Grignard starting materials, thus broadening the scope of this methodology towards a variety of electron-rich[154] and hetero-arenes[155]. Specific examples from each group's work are shown in Scheme 70. Both group conditions tolerate an extended reactant scope and require short reaction times; however the high basicity and nucleophilicity of Grignard reagents limits the scope of compatible aryl substituents.



Scheme 70. Electrophilic fluorination of Grignard reagents by a) Beller[154] and b) Knochel[155].

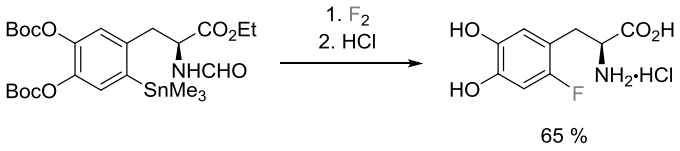
Unsurprisingly, organometallics with lower basicity such as aryl-silanes, -stannanes, -germanes and -boronic acids have greater functional group tolerance. However, they regularly require more reactive fluorine electrophiles such as elemental fluorine, XeF_2 or AcOF to facilitate fluorination, or are limited to electron-rich arenes (Scheme 71).[133,156,157]



Product	Yield (%)	Product	Yield (%)
	67		0
	100		75

Scheme 71. Electrophilic fluorination of aryl boronic acids with Selectfluor (55) is limited to electron-rich arenes.[133,156,157]

Elemental fluorine is commonly used for the preparation of 6-fluoro-*L*-DOPA (Scheme 72). When treated with $F_{2(g)}$ the trimethylstannane undergoes fluorodestannylation yielding the desired fluorinated product in a moderate-good yield of 65 % with good regioselectivity.[158] Despite the difficulty in handling F_2 it still remains one of the easiest and cheapest methods for introducing the short lived [^{18}F] isotope into a molecule, namely due to its high reactivity and hence fast incorporation time. This is exemplified by the successful preparation of the [^{18}F] analogue of 6-fluoro-*L*-DOPA (25 % RCY),[123a] which has been used as a PET-tracer in the investigation of Parkinson's disease[159] and in oncology.[160]



Scheme 72. Fluorodestannylation in the preparation of 6-fluoro-*L*-DOPA.[158]

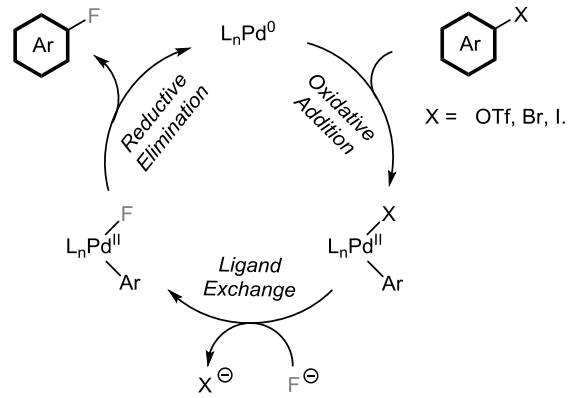
3.2.3. Pd catalysed fluorination

Transition metal catalysis has been widely used for the construction of carbon-heteroatom bonds including C–O, C–N, C–S, and C–P bonds.[161,162,163] However it was only recently that the construction of C–F bonds using transition metals was successfully achieved.[133,164] Grushin has carried out several mechanistic studies investigating the reductive elimination of Ar–F bonds from isolated Pd or Rh complexes [L_nMArF], demonstrating that Ar–F reductive elimination from these metal centres is extremely challenging.[165] As fluorine is the most electronegative element, it can form strong bonds to metals with significant ionic character. Consequently a reductive elimination pathway which results in Ar–F bond formation has a high barrier to activation.[166] However, more favourable

pathways often exist, precluding the Ar−F bond forming pathway and instead resulting in ligand-based P−F or C−F formation or the formation of stable $[L_nPdArF]_2$ dimers.[164b,167] Successful approaches to Ar−F bond formation from Pd commonly involve the use of ligands to promote reductive elimination from a Pd(II) centre. Alternatively, the $L_nPd(II)F$ complex can be oxidised to a more electron-deficient Pd(III) or Pd(IV) fluoride complex to promote C−F bond reductive elimination. The following section will focus on the mechanism and application of these processes.

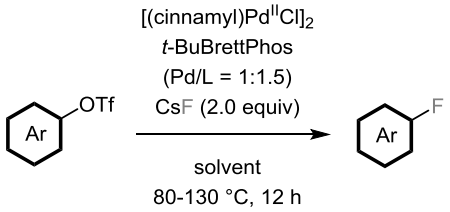
Ar−F bond formation from Pd(II) fluorides involving nucleophilic fluorine sources

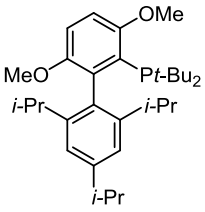
Pd-catalysed carbon-heteroatom bond formation can be broadly described as occurring via an oxidative addition-ligand exchange-reductive elimination catalytic cycle. Scheme 73 shows a general scheme for the formation of aryl fluorides via a Pd(0)/(II) mechanism involving a nucleophilic source of fluorine. As discussed previously, the reductive elimination step remains the most difficult step in the cycle. Grushin and Sanford have shown through the isolation of $L_nPd(II)F$ complexes, that Ar−F reductive elimination from Pd(II) is highly unfavourable and the thermolysis of these complexes results in biaryl homocoupling and no detection of the desired C−F coupling product.[165c,168]



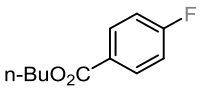
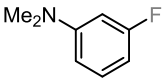
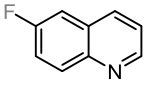
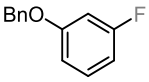
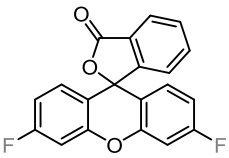
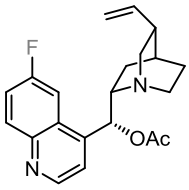
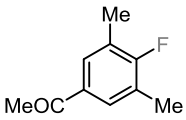
Scheme 73. General scheme of palladium-mediated aromatic nucleophilic fluorination.

In 2009, Buchwald and co-workers reported the first Pd-catalysed nucleophilic aromatic fluorination in addition to the first report of C—F reductive elimination from a Pd(II) complex.[164b,169,170] The initial reactions were low yielding despite requiring stoichiometric amounts of palladium-complex. The protocol was improved with the use of the stable Pd(0) precursor $[(cinnamyl)Pd^{II}Cl]_2$ with the bulky monodentate phosphine ligand '*t*-BuBrettPhos'[171] and CsF as the fluoride source. The optimised conditions permit the fluorination of a variety of substrates in good to excellent fluorination yields with sub-stoichiometric amounts of Pd, with an expansive substrate scope (Scheme 74). To date this remains the only example of catalytic aryl-fluoride formation involving a Pd(0)/(II) cycle and nucleophilic source of fluorine.





t-BuBrettPhos

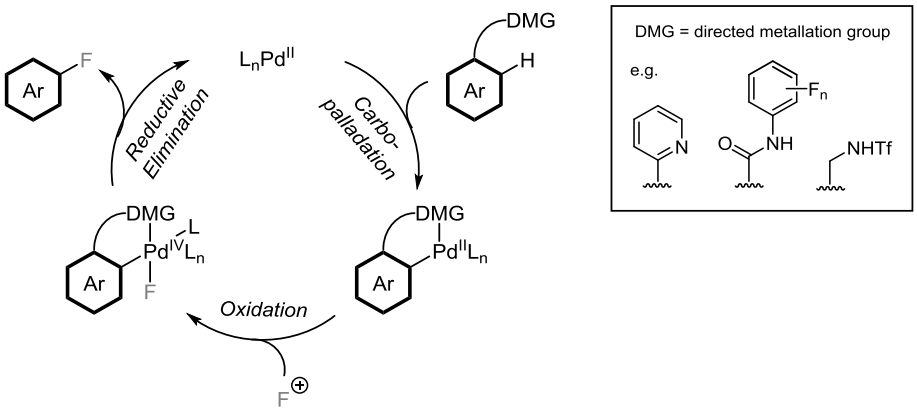
Product	Conditions	Yield (%)	Product	Conditions	Yield (%)
	toluene, 80 °C, [Pd] = 2 mol %	77		toluene, 110 °C, [Pd] = 4 mol %	73
	cyclohexane, 130 °C, [Pd] = 4 mol %	84		toluene, 120 °C, [Pd] = 2 mol %	78
	cyclohexane, 130 °C, [Pd] = 10 mol %	57		toluene, 110 °C, [Pd] = 8 mol %	73
	toluene, 110 °C, [Pd] = 10 mol %	70		toluene, 110 °C, [Pd] = 4 mol %	83

Scheme 74. Substrate scope and optimised conditions for the Pd-catalysed nucleophilic fluorination reported by Buchwald *et al.*[164b]

Ar–F bond formation from high valent Pd-fluorides involving electrophilic fluorine sources

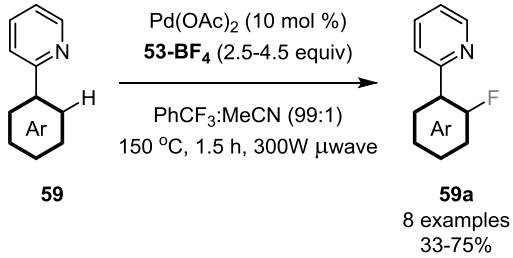
Recently, significant work has been carried out in the field of Pd-catalysed fluorination utilising electrophilic sources of fluorine. Fluoronium sources (such as those shown in Scheme 68) are highly oxidising and can oxidise Pd(II) complexes to Pd(IV) fluorides. Employing a Pd(II)/Pd(IV) catalysed approach to Ar–F formation has a two-fold benefit. Reductive elimination of a C–F bond from a Pd(IV) fluoride is more facile than from a Pd(II) fluoride,[172] and following C–F bond formation, the

resulting Pd(II) complex can participate in C−H activation. This approach allows for the development of C−H fluorination methodologies thus eliminating the need for pre-functionalised halide or pseudo-halide starting materials. One route to C−H fluorination uses a directed metallation group approach. Both Sanford and Yu have reported directed C−H fluorinations using pyridine,[173] triflamide[174] or removable aryl amide[175] auxiliaries (Scheme 75).



Scheme 75. General scheme of Pd-catalysed directed C−H fluorination with electrophilic fluorinating agents.

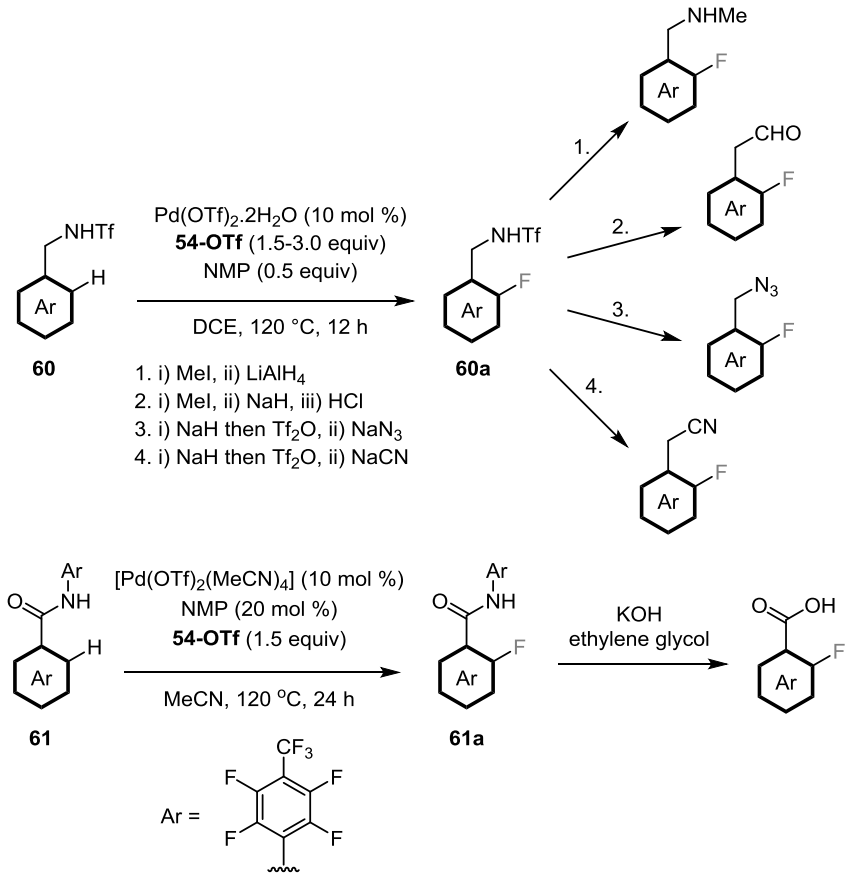
Pd catalysed directed C−H fluorination involving electrophilic fluorine sources are hypothesised to occur through a cyclopalladation-electrophilic fluorination cycle, involving oxidation to and reductive elimination from a high-valent palladium fluoride complex (Scheme 75).[viii] The first example was reported by Sanford *et al* in 2006, with the procedure yielding fluorophenyl pyridines in moderate to good yields (33-75 %) in short reaction times (<2 h) (Scheme 16).[173] These initial reports by Sanford and co-workers were groundbreaking, but the protocol requires high temperatures and microwave irradiation and only phenyl-pyridine systems (**59**) are reported for aromatic fluorination.



Scheme 76. Pd-catalysed electrophilic fluorination of phenyl pyridines **59** reported by Sanford *et al*.[173]

[viii] The mechanism of C−H functionalisation to form C−C or C−Het bonds has been hypothesised to involve reductive elimination from Pd(III) and Pd(IV) centres. However, Sanford *et al.* have reported the C(aryl)−F reductive elimination from a Pd(IV)−F complex, formed from oxidation of Pd(II) with electrophilic fluorine sources.[176]

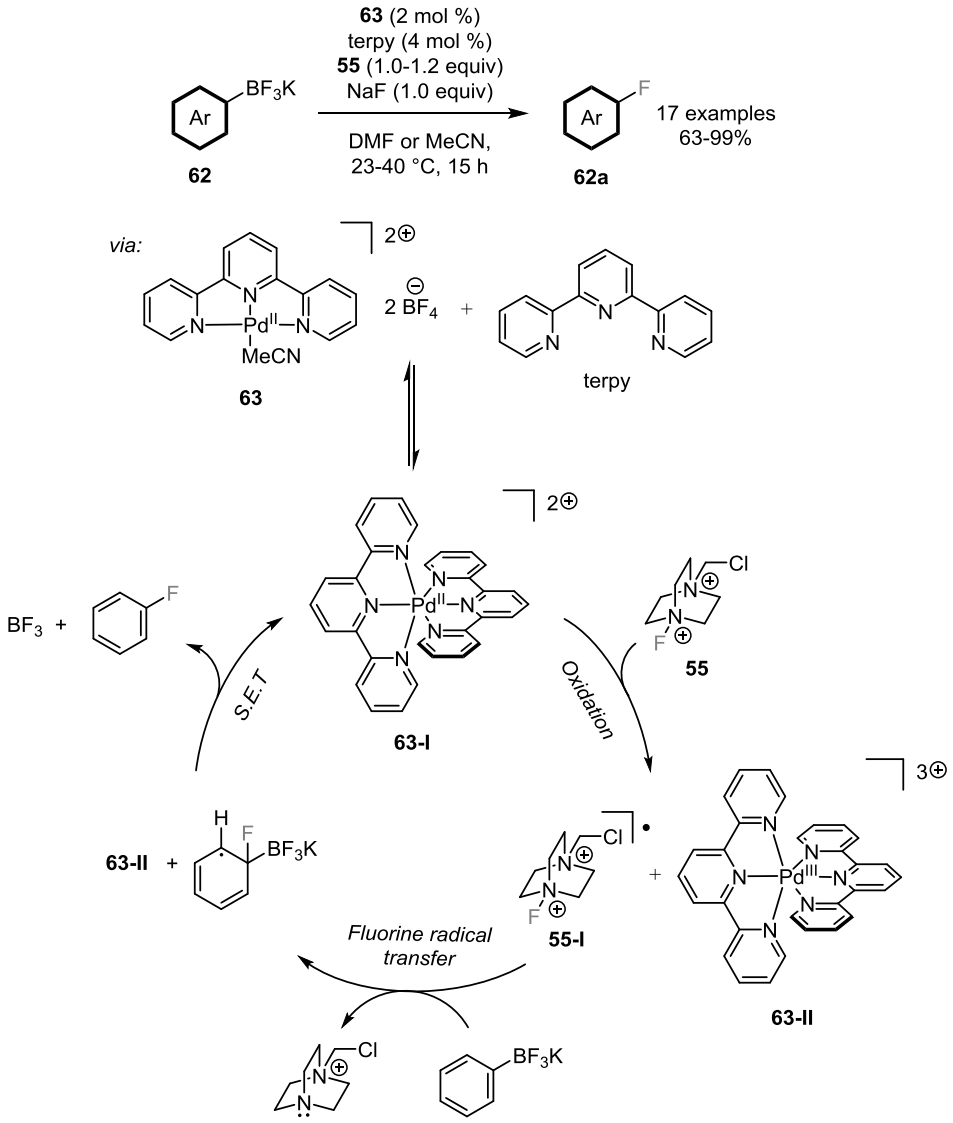
Recently Yu and co-workers reported the directed C–H fluorination of triflamide (**60**) and perfluorinated aryl amide (**61**) derivatives (Scheme 77).[174,175] Both methodologies utilise NMP as a promoter, the role of which was not investigated but may act as a base to deprotonate the acidic amide directing groups allowing coordination of the Pd centre, or as a ligand. Both protocols are robust, allowing aryl fluoride formation in consistently high yields without the need for microwave irradiation.



Scheme 77. Pd-catalysed *ortho*-fluorination of triflamide (**60**) and perfluorinated aryl amide (**61**) derivatives by *et al.*[174,175]

Although the triflamide auxiliary is not a particularly useful synthetic handle, it can be readily converted into a variety of different functionalities after fluorination and the perfluorinated aryl amide group can be readily hydrolysed to the carboxylic acid (Scheme 77).[174] This work was subsequently expanded by Xu, Xu and co-workers to include the fluorination of quinoxaline, pyrazole, benzoxazole and pyrazine derivatives using $Pd(OAc)_2$ as the catalyst.[177]

An alternative approach to Pd-catalysed fluorination in the presence of electrophilic fluorine sources involves the use of prefunctionalised aryl-boronic acid derivatives. Although this route requires the prior synthesis of the substrate and increases the amount of waste products, it allows for rapid regioselective reactions, which is imperative for the incorporation of the short-lived [^{18}F] isotope into tracer molecules.

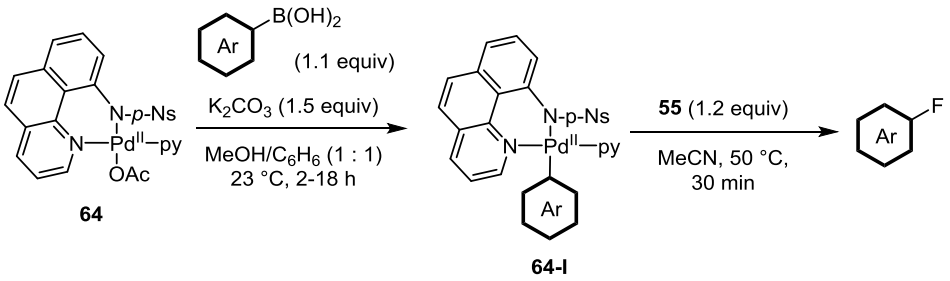


Scheme 78. Pd-catalysed fluorination of aryl potassium trifluoroborate salts (**62**) using Selectfluor **55** and the Pd(II)-terpy catalyst **63**, reported by Ritter and co-workers.[178a]

Recently, Ritter and co-workers have reported the electrophilic fluorination of aryl boronic acid derivatives using sophisticated palladium precatalysts.[178] The catalytic fluorination of aryl potassium trifluoroborate salts could be achieved at ambient temperatures via a Pd(II)/Pd(III) catalytic cycle (Scheme 78).[178a] The reaction is thought to proceed via a turnover limiting oxidation of the cationic Pd(II) complex **63-I** by Selectfluor to the well-defined Pd(III) catalyst **63-II**. Fluorine radical transfer from the reduced Selectfluor species **55-I** to the aryl-BF_3K salt forms the C–F resulting in a delocalised radical. Finally single electron transfer and loss of BF_3 forms the aryl fluoride product **62a** and regenerates the Pd(II) catalyst **63-I**.

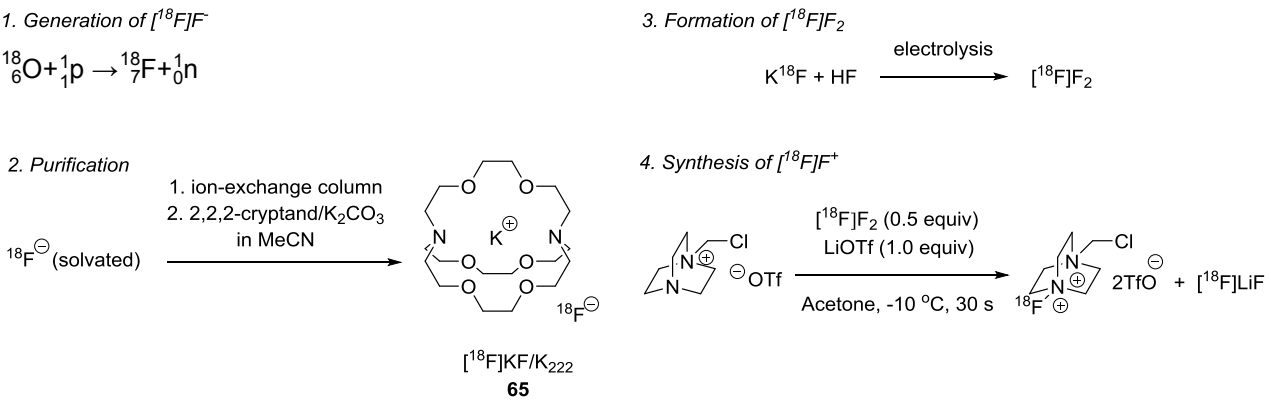
The stepwise fluorination of aryl boronic acids was also reported via the formation of an isolable aryl-Pd(II) complex **64-I** (Scheme 19).[178b] Following transmetallation, treatment of the aryl-Pd(II) complex **64-I** with **55** results in rapid C–F bond formation. The mechanism of reaction has not been

elucidated but may occur via electrophilic cleavage of the Ar–Pd bond or via reductive elimination from a high-valent Pd complex. Ritter and co-workers later commented that in this study a high-valent Pd species could not be observed by NMR.[133] However this does not rule out the intermediacy of such a species, as they subsequently showed the oxidation to and reductive elimination from a Pd(IV) complex with an enhanced ligand system.[179]



Scheme 79. Rapid fluorination of an isolable aryl-Pd(II) complex **64-I** reported by Ritter *et al.*[178b]

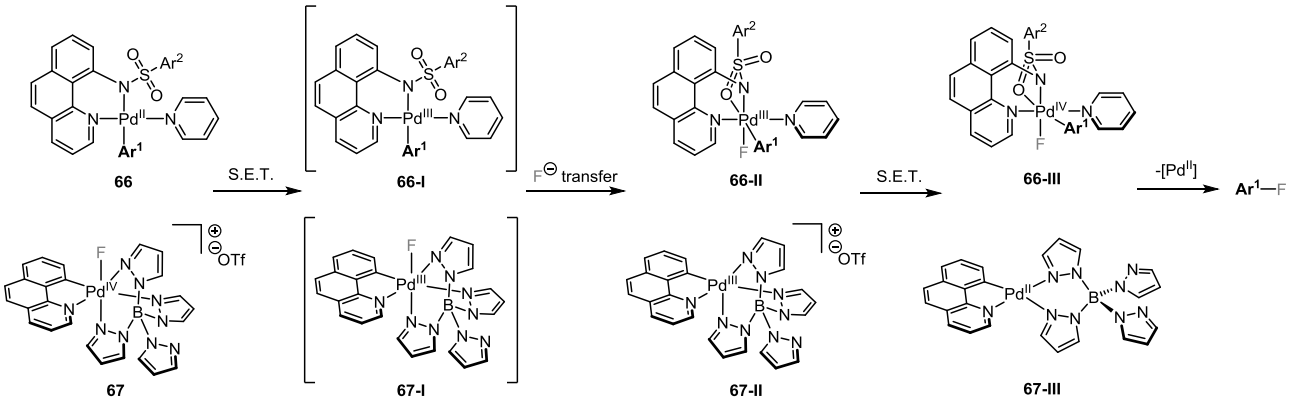
Although Ritter's protocol (Scheme 79) requires the formation of the aryl-Pd complex prior to fluorination, the route allows for rapid incorporation, which is a prerequisite for ^{18}F fluorination. However the use of $^{18}F^+$ sources is less desirable as the formation of ^{18}F-enriched Selectfluor requires several steps (Scheme 80). After aqueous $^{18}F^-$ is generated in a cyclotron or particle accelerator via a (p,n) knockout reaction it has to be separated from H_2O by an ion-exchange column. Following purification, $[(crypt\text{-}222)K]^+[^{18}F^-]$ (**65**) is obtained with a maximum theoretical radiochemical yield (RCY) of 100%. To convert fluoride into fluoronium it must be first electrolysed with HF to generate $[^{18}F]F_2$. However this results in reduction of RCY by at least 50%. The ^{18}F enriched fluorine gas can now be used to make $[^{18}F]$-Selectfluor. As ^{18}F has a half-life of 110 mins, the additional manipulations required to generate $^{18}F^+$ from $^{18}F^-$ result in a huge reduction in RCY before C–F bond formation can take place, so a protocol which utilises fluoride for rapid C–F bond formation is more desirable.



Scheme 80. Routes to $[^{18}F]$ fluoride and fluoronium.

Ar–F bond formation from high valent Pd fluorides involving nucleophilic fluorine sources

As previously discussed, aryl-F bond formation involving Pd catalysis and nucleophilic sources of fluorine is hindered by sluggish reductive elimination of the C–F bond from the Pd(II) fluoride. Recently Ritter and co-workers managed to circumvent this problem by designing a Pd complex which can act as an electrophilic fluorinating reagent by first 'capturing' fluoride then transferring it to a nucleophilic Pd(II) complex, in turn forming a Pd(IV) fluoride which can subsequently undergo C–F reductive elimination (Scheme 81).[180]



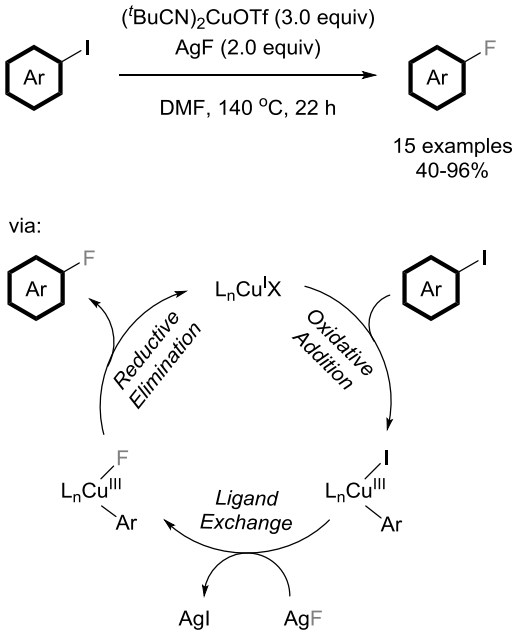
Scheme 81. Ritter *et al.* reported an aryl fluoride forming methodology involving two preformed Pd complexes (**66** and **67**). Complex **67** acts as an electrophilic fluorinating agent but is formed from a fluoride source. This approach has been used for rapid [^{18}F] incorporation.[180]

The protocol described in Scheme 81 by Ritter *et al.* permits the rapid fluorination of the Pd(II) complex **66** in 10 mins at 85 ^{o}C. The methodology has also been utilised for radiofluorination as the fluorine transfer agent **67** can be generated in 5 mins at 50 ^{o}C via fluoride displacement of a pyridyl ligand. Unfortunately the formation of complex **66** is slow and requires 10 hours for arene transmetallation to occur from the boronic acid starting material. This means that for [^{18}F] incorporation at least, a catalytic turnover in either metal cannot be achieved at this moment.

3.2.4. Cu catalysed fluorination

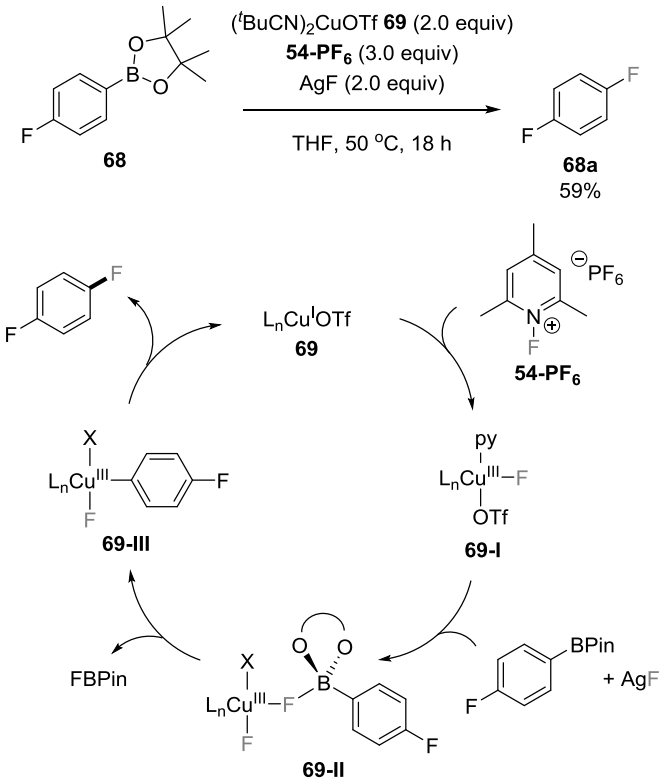
Recently a number of fluorination methodologies have been reported which utilise copper complexes to facilitate aryl fluoride formation. High valent copper complexes are more easily accessed than high valent palladium complexes.[172] Furthermore, reductive elimination of C–F bonds from Cu(III) fluorides is reported to be facile.[181,182,183] When these points are taken into account, in addition to the fact that Cu complexes can participate in analogous transformations to those reported with Pd; high valent Cu catalysis presents an attractive and potentially cheaper alternative to current Pd catalysed routes.

In 2012, Hartwig and co-workers reported the Cu-catalysed formation of aryl fluorides in good to excellent yields, starting from aryl iodides. The reaction follows a similar profile to Buchwald's original Pd-catalysed nucleophilic fluorination methodology,[164b] but without the requirement of a complex ligand system, albeit using super-stoichiometric amounts of copper salts (Scheme 82).



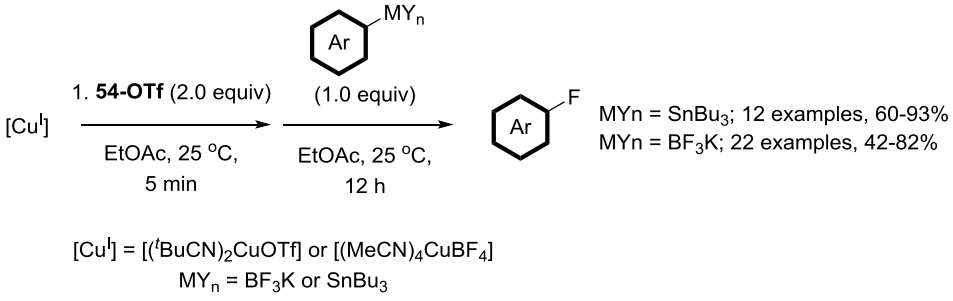
Scheme 82. Cu-catalysed nucleophilic fluorination of aryl iodides reported by Hartwig *et al.*[182a]

In a following publication, the protocol was improved with the use of boronic ester and an electrophilic fluorine source which permitted reaction at much lower temperatures (50 °C, cf. 140 °C), as shown in Scheme 83).[182b] The reaction is hypothesised to occur via initial oxidation of the nitrile copper complex **69** to Cu(III) fluoride **69-I**. This process was found to occur rapidly when a control experiment was carried out involving treatment of **69** with a suspension of **54-PF$_6$** in THF, at room temperature. After 5 min reaction a homogenous solution was obtained; ^{1}H and ^{19}F NMR spectroscopic and ESI-MS measurements revealed the presence of a new species which was characterised as Cu(III) fluoride complex **69-I**, however isolation attempts proved unsuccessful. Subsequent reaction of the THF solution containing the putative complex **69-I** with 4-fluorophenylboronate **68** at 50 °C resulted in no conversion after 18 h. However, when the reaction was repeated with the addition of AgF, the rapid formation of a new species was observed with >90 % conversion of **68** in 20 min. The new complex was analysed by ^{1}H, ^{19}F and ^{11}B NMR and determined to be **69-II**. As the reaction proceeded, the peak on the ^{11}B NMR attributed to complex **69-II** decayed with concomitant formation of FBPin. *In lieu* of this observation the transmetallation of the aryl group from boron to the Cu centre (**69-II** → **69-III**) is considered rate-limiting.



Scheme 83. Improved Cu-catalysed methodology reported Hartwig *et al.* using aryl pinacolboronate esters and the electrophilic fluorine source **54-PF$_6$**[182b]

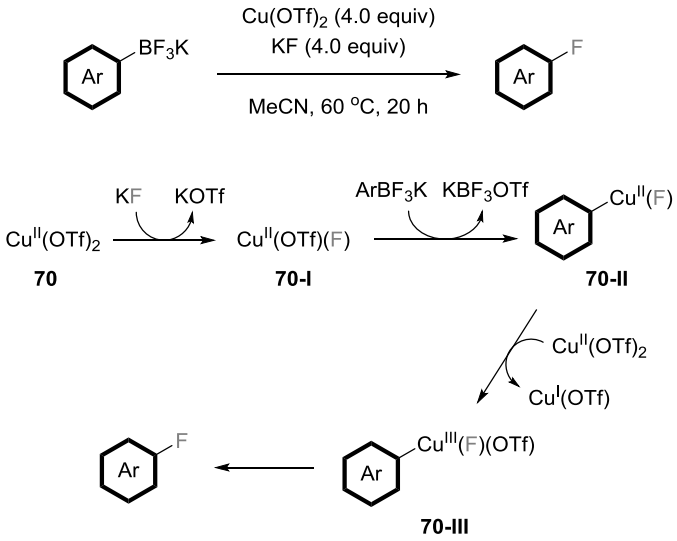
The requirement of AgF as the base in Hartwig's protocol is intriguing. The intermediacy of an aryl-Ag complex was ruled out as no reaction occurs in the absence of copper, and fluorination can be facilitated with other fluoride sources (e.g. KF, CsF), albeit with reduced yields (KF = 24%, CsF = 38%, cf. AgF = 75%). Electrophilic fluorine sources are susceptible to base-induced decomposition[184] and reaction with stronger alkoxide bases gave poor yields (10-15%). In addition, fluoride sources with increased solubility gave moderate yields. As a result, the superiority of AgF in the reaction is proposed to be a combination of its low solubility and low nucleophilicity. These factors allow transmetallation of the aryl group to Cu(III) but prevent transmetallation of the ArBPin to Cu(I), and furthermore, no appreciable decomposition of the F^+ source occurs, permitting oxidation of Cu(I) to Cu(III) to happen first.



Scheme 84. Stepwise Cu-mediated electrophilic fluorination of aryl boronates and stannanes reported by Sanford *et al.*[185]

In 2013, Sanford and co-workers reported the low temperature fluorination of aryl boronates and stannanes (Scheme 84) using a similar Cu/F^+ system to that reported by Hartwig *et al.* (Scheme 83).[185] The stepwise addition of the fluoronium source and organometallic reagent was required to ensure good yields. Without this tactic large amounts of biaryl are formed. The reaction does work with other neutral boronic acid derivatives (BPin, $B(OH)_2$, MIDA etc) but potassium trifluoroborate salts (BF_3K) give the highest yield, presumably due to the fact that they do not require nucleophilic activation to undergo transmetallation.

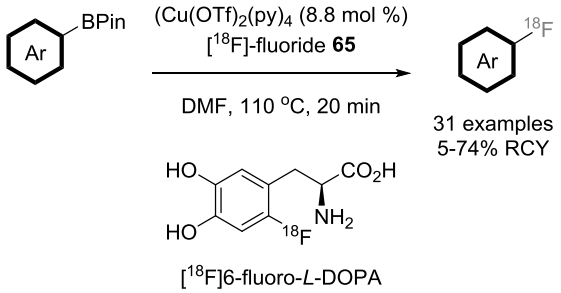
In a subsequent publication, Sanford *et al.* reported the fluorination of aryl-BF_3K salts in the presence 4 equiv of $Cu(OTf)_2$ and KF, without the addition of an exogenous oxidant (Scheme 85).[186] In this case the reaction is thought to proceed via initial ligand exchange of the fluoride source to form a Cu(II) fluoride **70-I**; this then transmetallates with the aryl-BF_3K salt to form an aryl-Cu(II) fluoride complex **70-II**, which is subsequently oxidised to Cu(III) (**70-III**) by another molecule of copper(II)triflate and undergoes reductive elimination in the product forming step generating copper(I)triflate. Ribas and Stahl have shown that analogous oxidative Cu-catalysed functionalisations can be carried out with sub-stoichiometric amounts of Cu(II) salts using dioxygen as the terminal oxidant.[187].



Scheme 85. Cu-mediated nucleophilic fluorination of $ArBF_3K$ salts reported by Sanford *et al.*[186]

The transformations reported by Sanford (Scheme 85) follow a similar reaction profile involving the generation of an aryl-Cu(II) species which is oxidised to Cu(III) by another molecule of Cu(II), following reductive elimination of the product Cu(I) is generated. In the case of Ribas and Stahl this Cu(I) salt can be oxidised to a catalytically active Cu(II) complex which can participate again in the catalytic transformation.[187] Unfortunately Sanford *et al.* report that the use of O_2 to render a

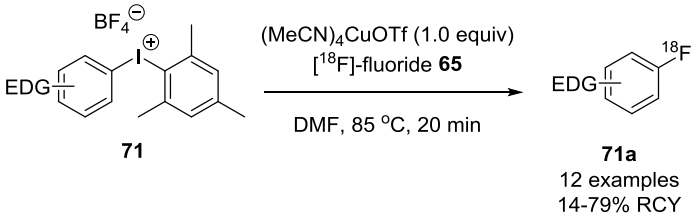
catalytic turnover proved unsuccessful;[186] in view of this, the requirement of a large excess of Cu is the major limitation of this protocol.



Scheme 86. Gouverneur and co-workers have reported the Cu-catalysed radiofluorination of aryl pinacol boronate esters. This methodology has been employed for the synthesis of [^{18}F]6-fluoro-*L*-DOPA.[188]

Recently, Gouverneur and co-workers reported the radiofluorination of aryl-pinacolboronate esters using catalytic amounts of Cu(II) salts (Scheme 86).[188] The protocol shows a wide substrate scope including examples of heteroarene fluorination and was adopted towards the formation of a clinical dose of [^{18}F]fluoro-*L*-DOPA. The reported reaction is carried out under air atmosphere and it is likely that the aerobic conditions and higher reaction temperatures (compared to Sanford's approach in Scheme 85) permit the turnover limiting oxidation of Cu(I) to Cu(II) to occur; as a result, sub-stoichiometric amounts of Cu salts can be used.

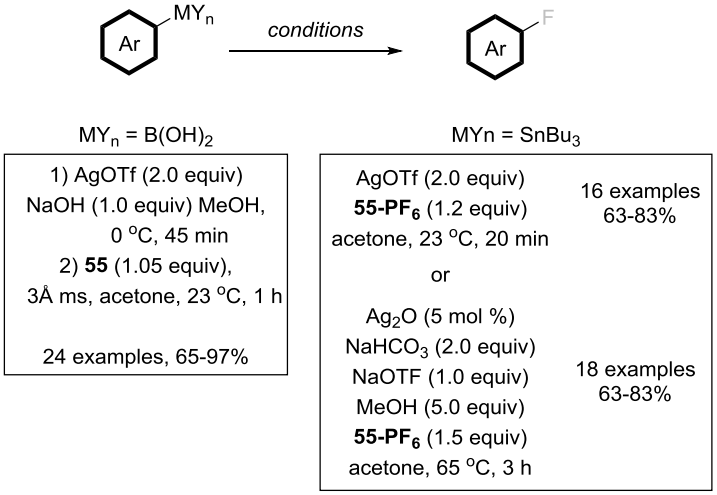
Another aromatic [^{18}F]fluorination protocol was also recently reported by Sanford *et al.*, utilising diaryliodonium salts (Scheme 87).[189] The transition metal free radiofluorination of thienyl-phenyliodonium salts has been previously achieved, however high temperatures are required (150 °C) and the reaction results in modest yields and a mixture of fluorinated products.[190] The Cu catalysed methodology reported by Sanford and co-workers uses mesityl iodonium salts (**71**) and results in high regioselectivity with fluorination occurring on the less bulky group, independent of electronics.



Scheme 87. The Cu-catalysed radiofluorination of diaryliodonium salts reported by Sanford *et al.*[191]

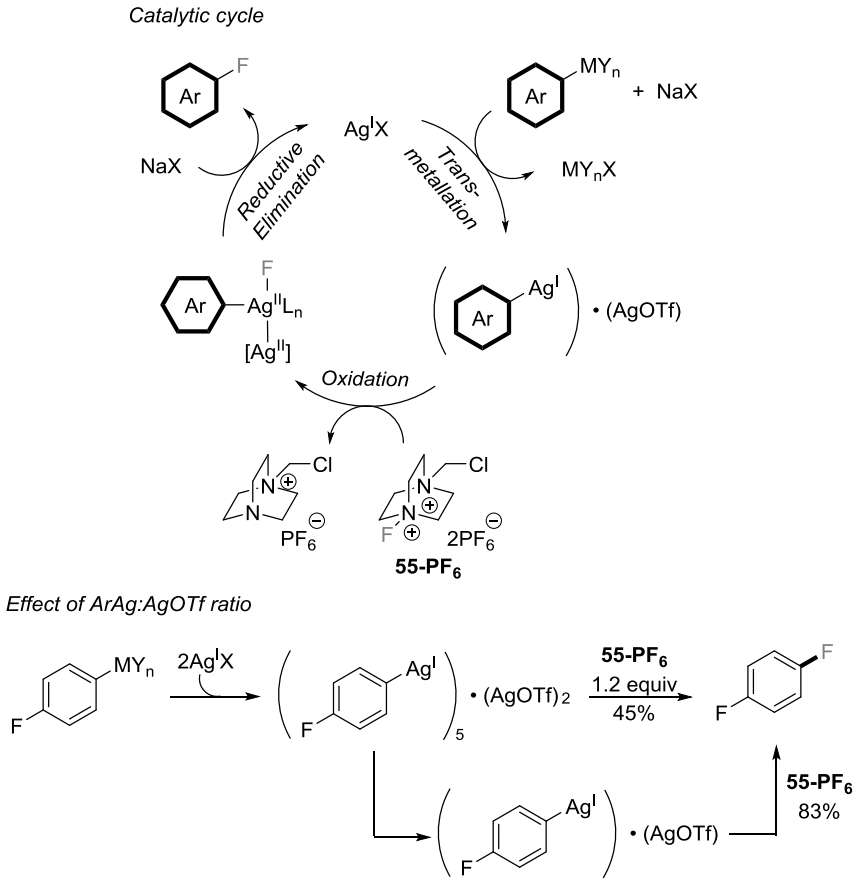
3.2.5. Ag catalysed fluorination

Recently, Ritter and co-workers reported the use of silver salts for the fluorination of an extensive array of aryl boronic acids[192] and stannanes[193] (Scheme 88). This work built upon previously described procedures by Lemaire[194] and Barrio[158,159] for the electrophilic fluorination of boronates and stannanes, respectively. The work by Ritter *et al.* presents a much wider substrate scope, and in some cases, much milder reaction conditions.



Scheme 88. An overview of the Ag-catalysed fluorination of aryl boronic acids and stannanes reported by Ritter *et al.*[192,193]

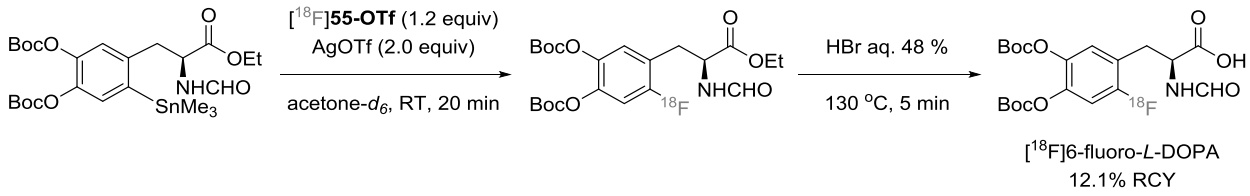
The protocols described in Scheme 88 are thought to proceed via a bimetallic oxidation reductive elimination process, as outlined in Scheme 89. The reaction proceeds via initial transmetallation of the organometallic reagent to the Ag(I) catalyst forming a complex with AgOTf. Control experiments by Ritter *et al.* showed that the best fluorination yields are afforded when an equimolar ratio of aryl-Ag to AgOTf is present; if this proportion of silver species are not achieved a polymeric silver complex is formed which was found to be less effective in the reaction. The bimetallic ArAg:AgOTf complex is then oxidised by **55-PF$_6$** to a bimetallic Ag(II) species which subsequently undergoes reductive elimination forming the product.[193] When the reaction was carried out using boronic acids, no yields were reported with sub-stoichiometric amounts of Ag, however 1.0 equiv of Ag gave a worse conversion compared to the optimal 2.0 equiv (43% and 82% yield of *p*-fluorobiphenyl, respectively).



Scheme 89. Proposed mechanism of silver-mediated electrophilic fluorination.[193]

Initially, for the reaction involving stannanes, the optimal amount of AgOTf was found to be 2.0 equiv (*p*-fluorophenyl = 83%). Lowering the amount of Ag to 1.0 equiv and 10 mol % gave *p*-fluorophenyl in 68% and 36% (3.6 turnovers), respectively. A catalytic turnover was observed and increasing the temperature (RT → 65 °C) improved conversion but resulted in large amounts of proto-destannylation product. Subsequent optimisation of the reaction conditions with the addition of NaOTf and $NaHCO_3$ allowed the fluorination of aryl stannanes using 5 mol % Ag_2O to occur in good to excellent yields in only 3 h at 65 °C.

Recently, Gouverneur and co-workers have adapted Ritter's fluorodestannylation methodology towards the radiofluorination of 6-fluoro-*L*-DOPA (Scheme 90).[195]



Scheme 90. The [^{18}F] labelled Selectfluor analogue **55-OTf** was used by Gouverneur *et al.* in the rapid generation of [^{18}F]6-fluoro-*L*-DOPA.[195]

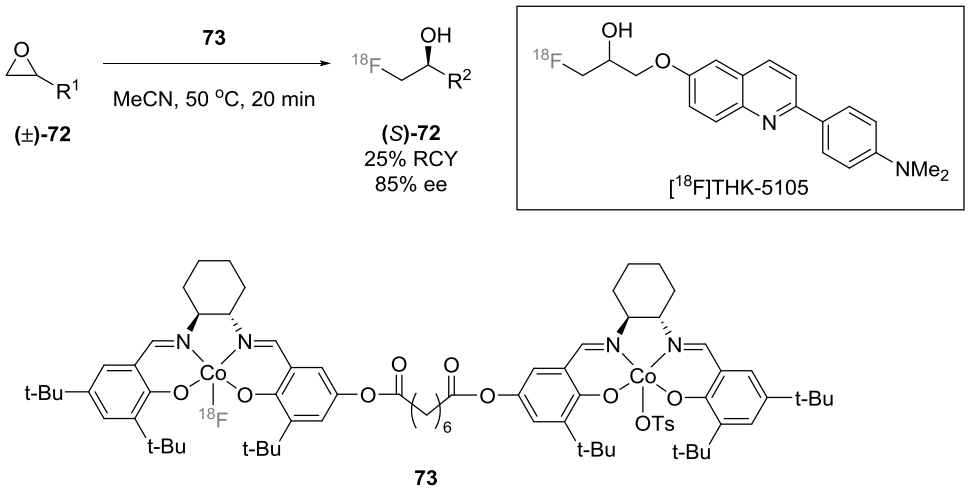
The silver-mediated fluorination protocols reported by Ritter and co-workers present a great step forward in both fluorination chemistry and silver catalysis, and have been applied to the late stage fluorination of complex organic molecules; however there are still limitations to the procedures. The fluorination of aryl stannanes is the most widely explored and the reaction can occur in relatively short reaction times with low loadings of Ag catalyst; nonetheless the use of stannanes in chemical synthesis, especially towards pharmaceutical-derivatives, is thoroughly discouraged due to the high toxicity of tin-reagents and their by-products. The stannane fluorination methodology is also limited by the formation of a protodestannylation byproduct, which can cause purification difficulties. The use of less toxic aryl boronic acid and silane[196] starting materials presents an agreeable alternative to tin reagents and these reagents do not suffer from protodemetallation byproduct formation. However, super-stoichiometric amounts of silver salts are required, and although silver salts are relatively cheap and can be recovered and reused following the reaction,[196] a protocol which uses low loadings of Ag would be the more attractive.

3.3. CURRENT METHODOLOGIES FOR ALKYL FLUORIDE BOND FORMATION

Traditional routes to C(sp^3)–F bond formation commonly involve deoxyfluorination or substitution of activated ethers or alkyl bromides with sources of nucleophilic fluorine such as Deoxofluor, DAST or TBAF.[197] However, these reagents can be difficult to handle in terms of hygroscopicity (TBAF) and reaction with moisture (Deoxofluor, DAST), in addition to high cost. Recently a number of elegant protocols have been established to furnish C(sp^3)–F bonds, particularly those situated in the benzylic position, utilising transition metal catalysed or photochemical methods, and are discussed herein.

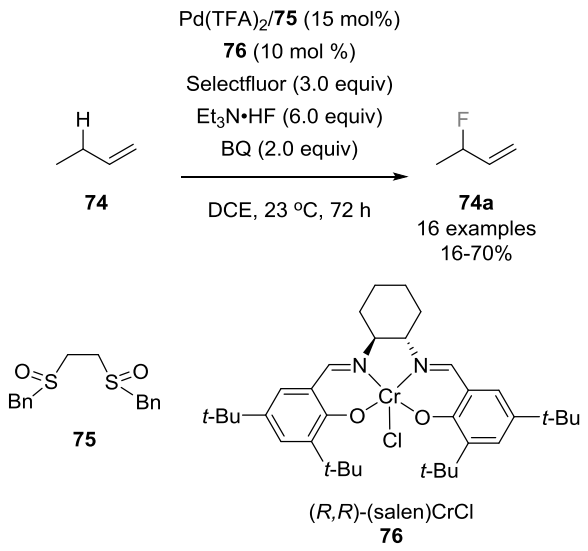
Transition metal catalysed (non-radical pathway)

Haufe and Doyle have shown that (salen)M catalysts can promote the fluoride ring opening of epoxides in a stereoselective manner.[198] Due to the importance of the [^{18}F]fluorohydrin motif in PET tracers, but the difficulties encountered in the radiolabelling of substrates with protic groups, Doyle and co-workers sought to expand the stereoselective fluoride ring opening of epoxides for the synthesis of radiolabelled fluorohydrins (Scheme 91).[199] Racemic epoxides (**72**) could be rapidly radiofluorinated using an air stable dimeric salen cobalt fluoride catalyst (**73**) under mild conditions. This approach was used for the synthesis of a number of PET tracer ligands including [^{18}F]THK-5105, an experimental PET tracer for imaging of tau pathology, an important biomarker for Alzheimer's disease.



Scheme 91. [^{18}F]fluoride epoxide ring opening was reported by Doyle *et al.* using a dimeric (salen)Co catalyst **73**. This methodology has been employed for the synthesis of a number of radio labelled fluorohydrin PET tracers.[199]

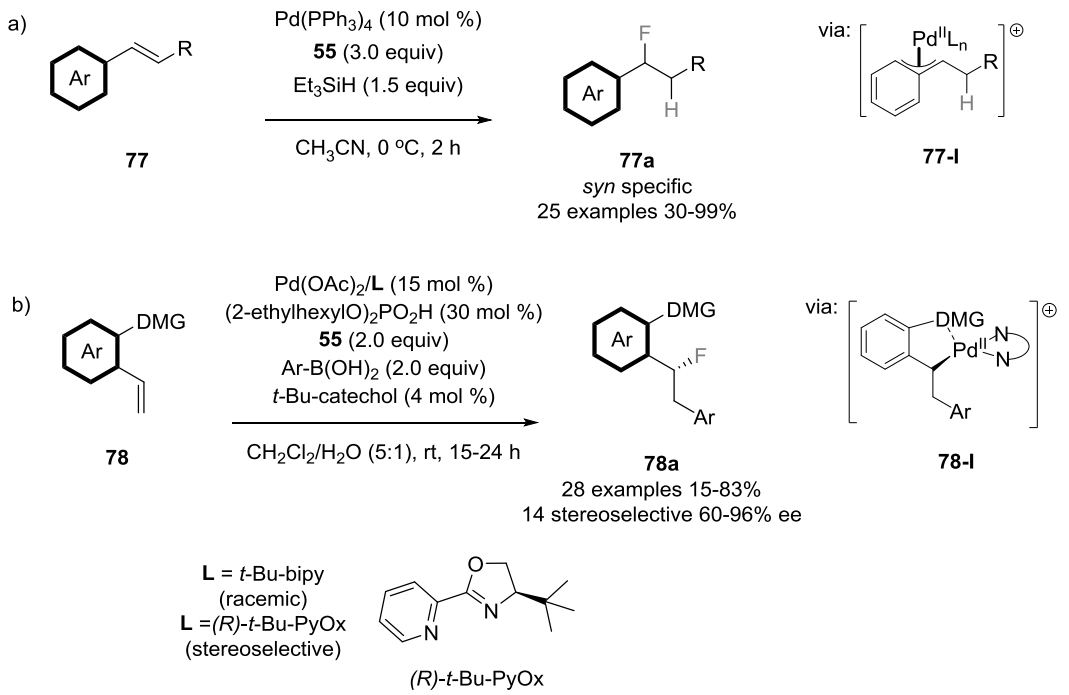
In the presence of Pd(0) salts, allylic compounds containing leaving groups form stabilised π-allyl complexes which can undergo substitution in the presence of a nucleophile forming a new C–C or C–Het bond. This interaction was first reported in 1965 by Tsuji and further developed by Trost in 1973.[200] Recently, a number of C(sp^3)–F bond forming reactions have been reported which exploit the substitution of *π*-allyl palladated intermediates using nucleophilic fluoride sources. A number of examples of allylic fluoride formation have been reported using leaving groups,[201] but in 2013 Doyle *et al*. reported the first catalytic allylic C-H fluorination (Scheme 92).[202] The protocol employs the use of a complex mixture of reagents but all are essential for good yield and regioselectivity. No reaction was observed in the absence of Pd, and little or no conversion occurs without the use of a bis-sulfoxide ligand (**75**); originally pioneered by White and co-workers,[203] and was shown to favour the formation of branched products in Pd-catalysed C-H allylic functionalisations. Furthermore, the Lewis acid co-catalyst (**76**) is required to activate the putative π-allylpalladium-BQ intermediate towards nucleophilic substitution (in this case with fluoride), an approach also pioneered by White and co-workers.[204]



Scheme 92. The first C−H allylic fluorination was reported by Doyle *et al.* using a dual Pd/sulfoxide and (salen)CrCl catalyst system.[202]

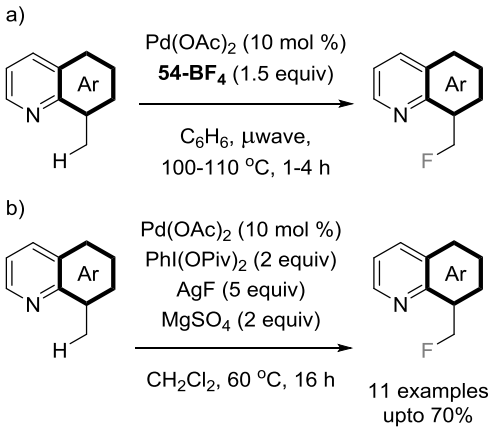
In the same vein, styrenes have been employed towards the formation of benzylic fluorides using palladium catalysis (Scheme 93). Gouverneur and co-workers reported the formal addition of H−F across the double bond in styrenes (**77**) via sequential addition of H^- then F^+ (Scheme 93a). The reaction is thought to proceed via addition of a palladium-hydride complex across the alkene to form η^3-benzyl complex **77-I**, which subsequently undergoes oxidation by Selectfluor (**55**), then reductive elimination to give the hydrofluorination product **77a**.[205]

Also in 2014, Toste *et al.* reported a remarkable Pd-catalysed fluoro-arylation of styrenes with **55** and arylboronic acids (Scheme 77b).[206] The reaction employs the use of a directing group on the arene, a phase-transfer catalyst [$(2\text{-ethylhexylO})_2PO_2H$], *t*-Bu-catechol as a radical scavenger and a bidentate ligand. The standard racemic reaction is carried out with a *t*-Bu-bipyridyl ligand alternatively the reaction can be rendered stereoselective using a simple *tert*-butyl substituted pyridyl-oxazoline ligand *(R)-t*-Bu-PyOx.



Scheme 93. Examples of Pd-catalysed C(sp^3)-H fluorination of styrenes by a) Gouverneur[205] and b) Toste[206].

Another example of Pd^{II}/Pd^{IV} catalysed C(sp^3)−H fluorination was reported in 2006 and 2012 by Sanford and co-workers.[207] Using 8-methylquinoline derivatives they carried out the Pd-catalysed directed intramolecular C−H fluorination of C(sp^3)−H bonds using both electrophilic sources of fluorine (Scheme 94a) and nucleophilic sources with an additional oxidant (Scheme 94b).

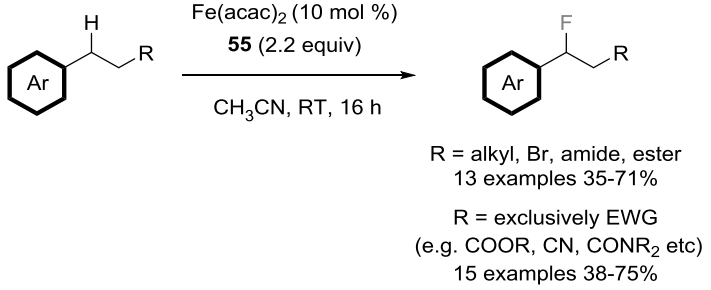


Scheme 94. Pd-catalysed C(sp^3)-H fluorination methodologies reported by Sanford *et al.* employing electrophilic[207a] and nucleophilic[207b] sources of fluoride.

Transition metal catalysed (radical pathway)

Benzylic C−H bonds exhibit enhanced reactivity over other unsaturated alkanes. The bond dissociation energy of the benzylic C−H bond in ethyl benzene lies between that of the C−Het bond in *tert*-butylchloride and *tert*-butanol.[ix] Moreover, the stabilising ability of the neighbouring π-system means that not only is the formation of a benzyl radical relatively facile, but once formed they are also relatively stable, in fact the most stable of all carbon radicals. In this context, there have been a number of recent reports of Bn−F bond formation via the generation of benzylic radicals followed by recombination with a source of radical fluorine or subsequent oxidation to the carbocation then reaction with fluoride.

In 2012 Lectka *et al.* reported a copper(I) bis-imine and *N*-hydroxyphthalimide co-catalysed fluorination of alkanes using Selectfluor as the fluorine source.[208] The reported catalyst system was efficient for the formation of alkyl-fluorine bonds but had limited applicability for benzylic fluorination. Accordingly, they found that a simple $Fe(acac)_2$ system showed enhanced reactivity for benzylic fluorination and furthermore was completely selective for activation of the benzylic position with no fluorination of simple alkyl centres observed (Scheme 95).[209] Preliminary experiments involving cyclopropane ring opening and cyclisation of alkenes indicate the involvement of radicals.[209b] However, it has not yet been ascertained whether the reaction proceeds via benzylic radical formation then fluorine radical abstraction from Selectfluor[210] or from a high valent iron-fluoride complex.[211]

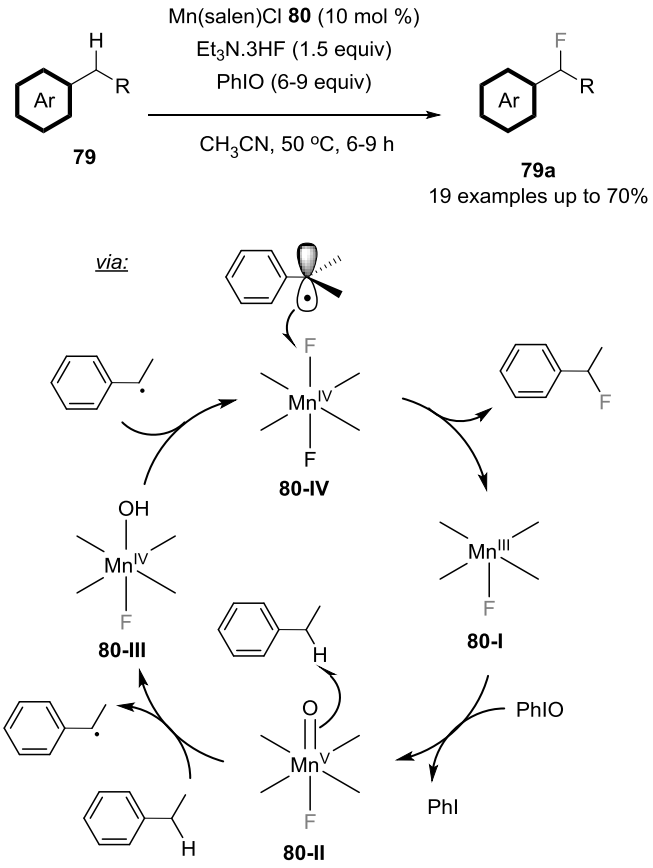


Scheme 95. Fe-catalysed C(sp^3)-H fluorination reported by Lectka *et al.*[209]

Recently, the Groves group reported the Mn-catalysed fluorination of alkanes using anionic fluorine sources.[211] Initially a modified porphyrin system was used for C(sp^3)−H bond fluorination however when applied to benzylic systems a mixture of fluorinated and oxygenated products were observed.[211] On screening different ligand systems the use of a Mn(salen)Cl catalyst (**80**) initially

[ix] Methyl benzene, benzylic C−H = 89.7 kJ mol^{-1} (± 2.5 kJ mol^{-1}); *tert*-butylchloride, C−Cl = 84.9 $kcalmol^{-1}$; *tert*-butanol, C−OH = 95.8 $kcalmol^{-1}$.[103]

developed by Jacobsen[212], allowed selective fluorination of benzylic positions over other aliphatic carbons (Scheme 96).

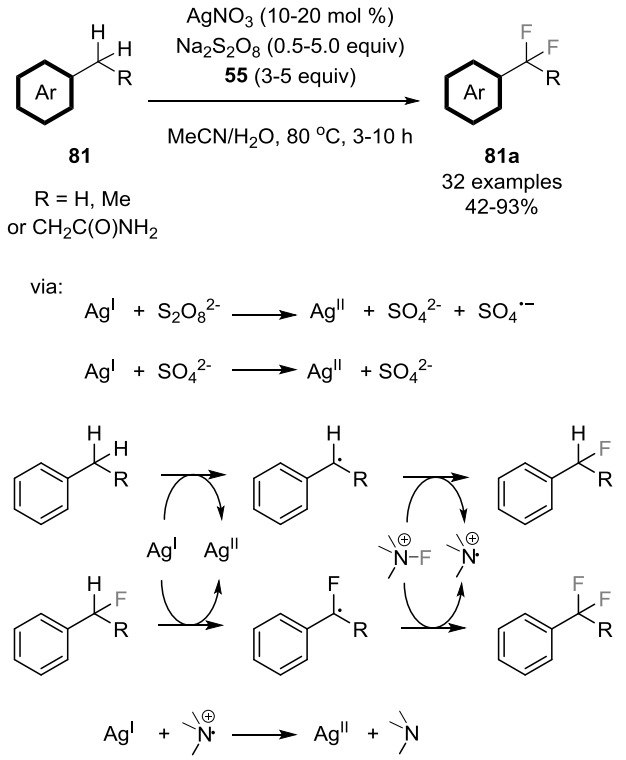


Scheme 96. Mn-catalysed C(sp^3)-H fluorination reported by Groves *et al.*[211]

The proposed reaction mechanism is depicted in Scheme 96 and involves initial halide ligand exchange in the presence of AgF or TREAT.HF ($Et_3N.3HF$) to form a [Mn(salen)F] (**80-I**) or $[Mn(salen)F_2]^-$ complex, which is then oxidised to **80-II** by iodosylbenzene (PhIO). This manganese(V)oxo complex (**80-II**) abstracts a hydrogen radical from the substrate **79** which then undergoes fluorine transfer from the manganese(IV)fluoro complex **80-IV** forming the product **79a** and regenerating the catalyst **80-I**. The protocol tolerates a number of different functional groups and was applied to the late-stage fluorination of four bioactive molecules. However its main limitation is the lack of operational simplicity. Differing sources and amount of fluoride are required for different substrates which limits its practical application. Moreover a large excess (6-8 equiv) of oxidant is required which must be added portion-wise over several hours in order to achieve good yields.

In 2014, Tang and co-workers published a Ag-catalysed benzylic fluorination methodology (Scheme 97).[213] This was the first example of Ag-catalysed oxidative C−H fluorination at the benzylic position. Using Selectfluor as the fluorine radical source, they were able to access a number of

difluoromethylated arenes. The proposed reaction mechanism involves a Ag^{I}/Ag^{II} catalytic cycle employing two sources of oxidant, $Na_2S_2O_8$ and Selectfluor. The peroxydisulfate ion oxidises Ag(I) to Ag (II), and this high valent silver species abstracts a hydrogen atom from the benzylic position generating a benzylic radical with reacts with Selectfluor in the first fluorination step. Silver (I) can now be re-oxidised by a sulfate anion radical leftover from the first oxidation step or the aminium radical from the fluorination step; the hydrogen abstraction−fluorination cycle now reoccurs generating the difluoromethylated product **81a**. In products generated from methyl benzene (**81**, where R = H) no trifluoromethylation is observed, presumably due to the increased bond dissociation energy of the C−H adjacent to 2 fluorine atoms.

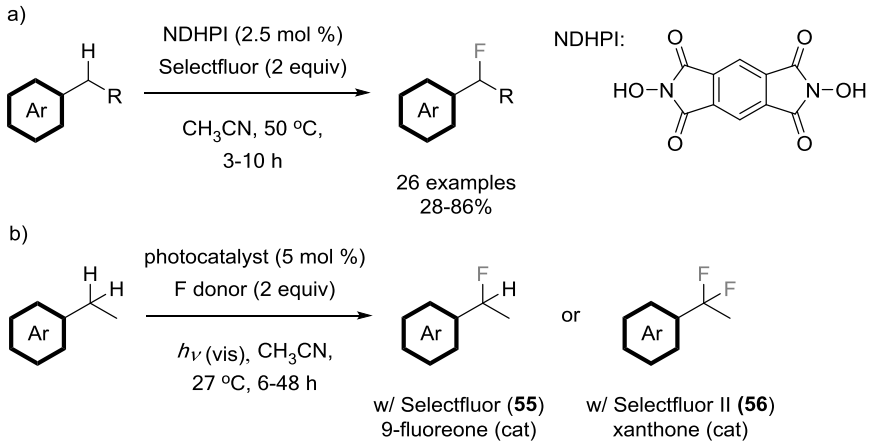


Scheme 97. Ag-catalysed C(sp^3)-H fluorination reported by Tang *et al.*[213]

Metal-free fluorination

In 2013, the groups of Inoue and Chen reported metal-free routes to benzylic fluorination. Inoue and co-workers investigated the different *N*-hydroxy compounds as sources of hydrogen radical abstractors for the generation of benzylic radicals. They found that low loadings of NDHPI in combination with Selectfluor permitted the formation of benzylic fluorides in good yields under mild conditions (Scheme 98a).[214]

Utilising visible light/diarylketone photocatalysis Chen and co-workers reported a remarkable ambient temperature benzylic C−H fluorination methodology (Scheme 98b).[215] The reaction exhibits excellent substrate scope and is high yielding; moreover, selective mono− or di−fluorination can be achieved depending on the choice of photocatalyst. Similar to the aforementioned examples of benzylic fluorination, the reaction involves the formation of a benzylic radical which subsequently fluorinates in the presence of Selectfluor. It is proposed that on loss of a fluorine radical, the aminium cation generated from Selectfluor helps to turn over the stable ketyl radical, regenerating the photocatalyst, consequently permitting low catalyst loadings.



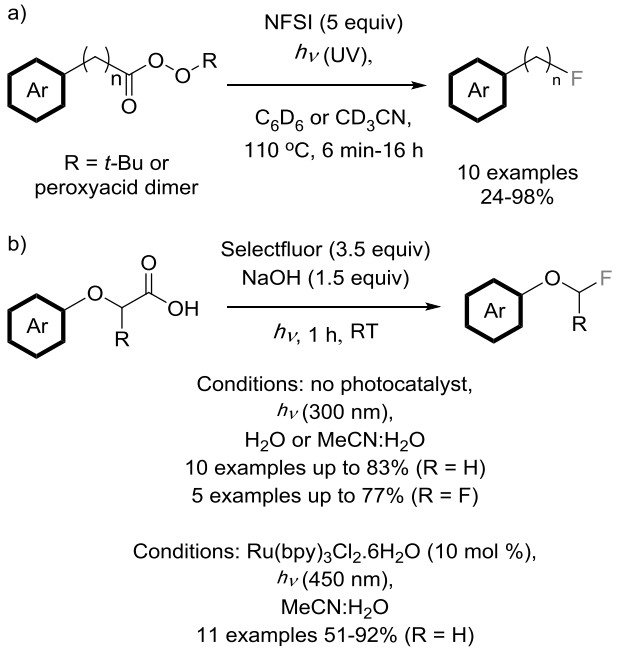
Scheme 98. Examples of metal-free C(sp^3)-H fluorination.[214,215]

Decarboxylative fluorination (photocatalysed)

Paquin and Sammis have demonstrated a number of examples of C(sp^3)−F bond formation by exploiting the tendency of electrophilic fluorinating agents to undergo fluorine transfer to alkyl radicals (Scheme 99). Initially they utilised per-oxy acids under UV irradiation to generate alkyl radicals via decarboxylation (Scheme 99a).[210] Through DFT studies they established that Selectfluor has the lowest BDE of the commercially available sources of electrophilic fluorine, however due to its poor solubility in organic solvents, NFSI was chosen and allowed for the fluorination of 10 substrates up to 98% yield, including a cholic acid derivative. As a proof of concept, this work was particularly informative however due to the requirement of large excesses of fluorinating agent and the preparation of potentially explosive starting material, its synthetic applicability is limited.

Subsequently, Paquin and Sammis reported the photoactivated decarboxylative fluorination of aryl-oxy carboxylic acids (Scheme 99b). By switching to aqueous solvent systems the less expensive Selectfluor could be used to fluorinate a number of substrates at ambient temperature in short

reaction times. The transformation can be carried out under UV light in the absence of a photocatalyst, only base is required to promote the reaction,[216] or under visible photocatalysis using $Ru(bpy)_3Cl_2.6H_2O$.

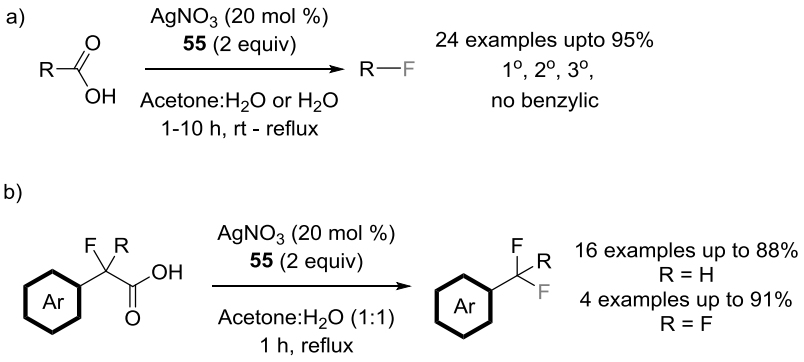


Scheme 99. Examples of photocatalytic decarboxylative C(sp^3)-F bond formation by Paquin and Sammis.[210,216]

Decarboxylative fluorination (Ag catalysed)

The Borodin-Hunsdiecker reaction is the most famous example of a decarboxylative halogenation that proceeds via a radical pathway. However, there a number of contraindications that limit its synthetic application, namely the requirement of stoichiometric amounts of stringently dried silver carboxylates and the use of corrosive or toxic reagents (eg. Br_2 and CCl_4).[217] In 2012, Li *et al.* reported the first catalytic Borodin-Hunsdiecker type reaction for the formation of alkyl-chlorides.[218] Subsequently this methodology was adapted for the formation of alkyl-fluorides (Scheme 100); in this work the authors report the several high yielding examples of fluorination of primary, secondary and tertiary alkanes, but no examples of fluorination at the benzylic position were reported.[219]

Gouverneur and co-workers employed similar reaction conditions for the formation of di- and tri-fluoromethylated arenes from the corresponding mono- or di-α-fluorinated phenylacetic acids. Due to the short reaction times they were able to employ this methodology for the formation of [^{18}F] labelled compounds using [^{18}F] enriched **55**.[220]



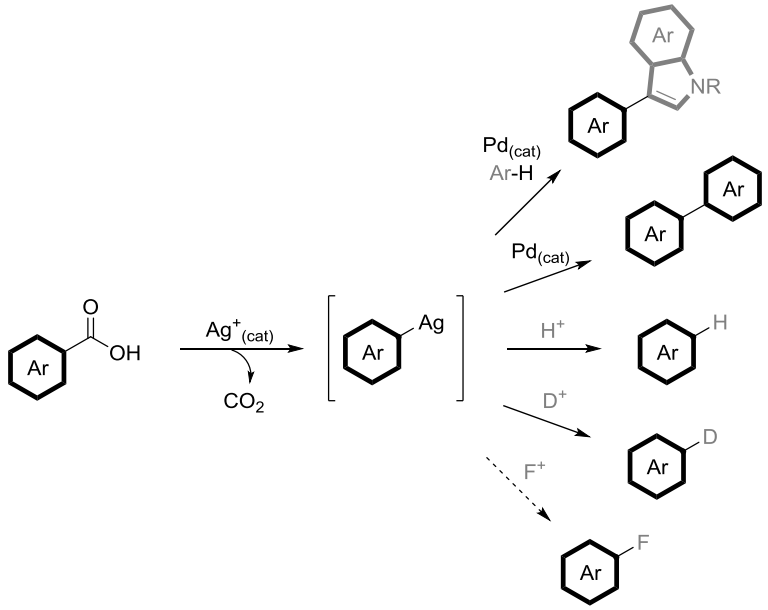
Scheme 100. Examples of Ag-catalysed decarboxylative C(sp^3)-F bond formation.[219,220]

3.4. DECARBOXYLATIVE FLUORINATION – ARYL FLUORIDE FORMATION

3.4.1. Aims of the project – Fluorination via a Ag(I) decarboxylation route

Fluorinated aromatic compounds have important applications in medicine for the formation of pharmaceutically active ingredients and for ^{18}F-labelled compounds in PET radiochemistry, and in materials and agrochemical sciences. However, regioselective incorporation of fluorine in organic molecules from simple readily available starting materials remains a challenge. Thus the development of a facile fluorination method would be of significant benefit.

Recently, Larrosa and others have shown that Ag salts can activate (hetero)aromatic acids to extrude CO_2 in turn generating reactive aryl-Ag intermediates. These reactive species are nucleophilic and can readily react with a variety of electrophiles or transmetallate to Pd and undergo cross-coupling pathways to generate a variety of hetero- or homo-biaryl scaffolds (Scheme 101).[x]



Scheme 101. Transition metal catalysed decarboxylative fluorination.

As discussed previously, Ritter and co-workers have shown that aryl boronic acids, stannanes and silanes can undergo fluorination via an Ag-catalysed pathway.[192,193,196] Hence, we envisage that the Ag-catalysed decarboxylation protocols developed in the group could be expanded to include the formation of Ar−F bonds. Ritter *et al.* have shown that the aryl-Ag intermediates generated from stannyl and boryl starting materials readily fluorodemetallate. Accordingly, not only does it seem viable that our methodology can be used for the formation of fluoroaromatics, but the generation of

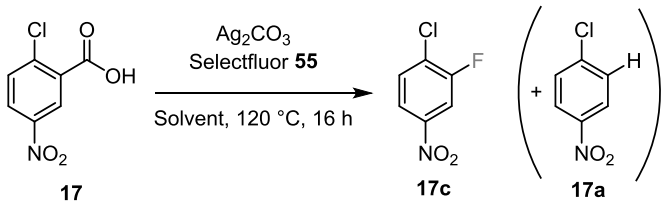
[x] These transformations are discussed in depth in Chapters 1 and 2.

aryl-Ag intermediates via a decarboxylative pathway is highly desirable, as carboxylic acids are cheap, readily available starting materials, whereas the current methodologies employ the use of substrates which are toxic and/or expensive and may require multi-step syntheses to access.

3.4.2. Optimisation attempts

The first approach to develop an Ag-catalysed decarboxylative fluorination methodology was to adapt the optimal conditions for the protodecarboxylation reaction (Ag_2CO_3 10 mol %, DMSO, 120 ^oC, 16 h), previously developed within the group,[25a] with the addition of F^+ sources (Table 1).

Table 9. Optimisation attempt of the fluoro- and proto- decarboxylation of 2-chloro-5-nitro-benzoic acid (**17**)[a]



Entry	Ag_2CO_3 (equiv)	Selectfluor (equiv)	Solvent	Product distribution[b,c] F (%)	Product distribution[b,c] H (%)
1	0.1	-	DMSO	-	<99
2	0.1	1.2	DMSO	0	0
3	1.0	-	DMSO	-	<99
4	1.0	1.2	DMSO	0	42
5	0.1	-	Acetone[d]	-	0
6	0.1	1.2	Acetone[d]	0	0
7	0.1	-	MeCN[d]	-	0
8	0.1	1.2	MeCN[d]	0	0
9	0.1	-	Acetone : DMSO (95:5)	-	0
10	1.0	1.2	Acetone : DMSO (95:5)	0	0
11	0.1	-	MeCN : DMSO (95:5)	-	78
12	1.0	1.2	MeCN : DMSO (95:5)	0	23
13	1.0	1.5	Benzene : DMSO (8:1)	0	0
14	1.0	1.5	Dioxane : DMSO (8:1)	0	0

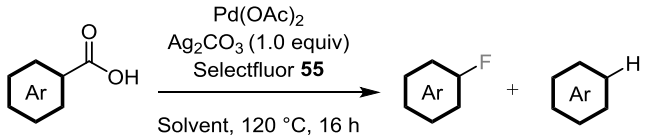
[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol **17**, Ag_2CO_3 and **55** (amounts as stated), using 0.5 mL anhydrous solvents (unless otherwise stated) in a 10 mL sealed vial. [b]Yields determined by ^1H NMR analysis using *p*-xylene as an internal standard. [c]Remaining mass balance is unreacted starting material. [d]Non-anhydrous, reagent grade solvents.

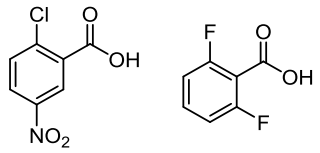
Using 2-chloro-5-nitro benzoic acid (**17**) as the optimisation substrate, the reaction conditions were screened using Selectfluor (**55**) as electrophilic fluorine source (Table 9). However, not only were no traces of product detected, but it was apparent that the presence of Selectfluor in the reaction mixture had a detrimental effect on decarboxylation, with no conversion observed after 16

h compared to the control protodecarboxylation which gave quantitative yield (Table 9, cf. entries 1 and 2). Next the amount of Ag_2CO_3 was increased to 1.0 equiv, and 42% protodecarboxylation observed in the presence of Selectfluor, but again no trace of the fluoroarene product **17c**. Different reaction solvents were screened which are commonly used in conjunction with Selectfluor (acetone and MeCN). However these solvents seem to be incompatible with the decarboxylation step with no conversion observed in the control protodecarboxylations (Table 9, entries 5 and 7). With the addition of 5% DMSO (v/v) the protodecarboxylation could be achieved in 78% using MeCN as the main solvent (Table 9, entry 11) and 10 mol % Ag_2CO_3. However, with the addition of Selectfluor and stoichiometric amounts of Ag_2CO_3 no trace of desired product was observed and a reduction in protodecarboxylation occurred. The addition of Selectfluor seems to have a negative effect on decarboxylation with no fluorination product observed, and a reduced amount of protodecarboxylation compared to the control reactions and unreacted starting remaining after reaction, even with super-stoichiometric amounts of Ag.

Under the reaction conditions the aryl-Ag intermediate may be formed then decomposes under the reaction conditions, before fluorination can occur. Fluorination from aryl-Pd intermediates has been shown to occur via a putative Pd(II/IV) cycle. Larrosa and co-workers have shown that aryl-Ag intermediates generated through a decarboxylative pathway can transmetallate to Pd(II) centre. In this vein, the reaction was carried out with the addition of 10 mol % $Pd(OAc)_2$ in the hope that the aryl-Ag intermediate can transmetallate to Pd which can then undergo a fluorodemetallation pathway. However, with the addition of 10 mol % $Pd(OAc)_2$ using the model substrate **17**, no fluorinated product was observed (Table 10, entries 4 and 5). Moreover no protodemetallation was detected with 1.5 equiv of Selectfluor where previously 23% and 42% was observed when MeCN:DMSO (95:5) and DMSO were used as the reaction solvents with 1.2 equiv of Selectfluor (cf. Table 9, entries 12 and 4, respectively). The reactions were also carried out with a different substrate, 2,6-difluorobenzoic acid **82**, to ensure that the lack of reactivity is not related to the substrate. This substrate decarboxylates even more rapidly than **17**, however no fluorinated product was observed with either the Ag/F^+ system or with additional $Pd(OAc)_2$ (Table 10, entries 2-3, 6-7, respectively).

Table 10. Optimisation attempt for the fluorodecarboxylation of 2-chloro-5-nitro-benzoic acid (**17**) and 2,6-difluorobenzoic (**82**) with the addition of $Pd(OAc)_2$[a]





17 **82**

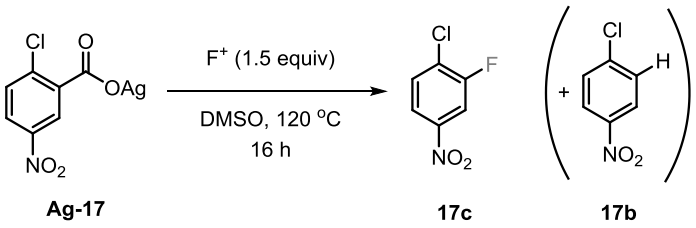
Entry	Arene	$Pd(OAc)_2$ (mol %)	SelectFluor (equiv)	Solvent	Product distribution[b,c]	
					F (%)	H (%)
1	**82**	-	-	DMSO	-	<99
2	**82**	-	1.2	DMSO	-	42
3	**82**	-	1.2	MeCN : DMSO (95:5)	-	23
4	**17**	10	1.5	DMSO	0	0
5	**17**	10	1.5	MeCN : DMSO (95:5)	0	0
6	**82**	10	1.5	DMSO	0	25
7	**82**	10	1.5	MeCN : DMSO (95:5)	0	0

[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of substrate, Ag_2CO_3, **55** and $Pd(OAc)_2$ (amounts as stated), using 0.5 mL anhydrous solvents in a 10 mL sealed vial. [b]Yields determined by ^1H NMR analysis using *p*-xylene as an internal standard. [c]Remaining mass balance is unreacted starting material.

The Ag-catalysed decarboxylation is thought to proceed via formation of a silver carboxylate which is rapidly generated via an acid-base reaction with Ag_2CO_3, or via ligand exchange with the potassium carboxylate and a silver salt. This resulting compound is catalytically active and forms the aryl-Ag intermediate on loss of CO_2.[xi] To investigate whether electrophilic fluorine is impeding decarboxylation by hindering either the silver carboxylate formation or the rate-limiting decarboxylation step, the silver carboxylate **Ag-17** was synthesised and reacted with the optimal reaction solvent (DMSO) and different commercially available F^+ sources (Table 11, entries 1-4). In every case no fluorinated product was detected and only a small amount of protodecarboxylation was observed with **53-OTf**. Although these reactions do not shed light on whether F^+ sources effect carboxylate formation, they do reveal that a variety of electrophilic fluorinating reagents, or at least some reactive species formed from them have a detrimental effect on the decarboxylation step.

[xi] See Chapter 1, Scheme 47 for a general catalytic cycle.

Table 11. Investigating the effect of F^+ sources on the decarboxylation of silver 2-chloro-5-nitro-benzoate (**Ag-17**)[a]



Ag-17 **17c** **17b**

Entry	F^+	Product distribution[b]	
		F (%)	H (%)
1	**51**	0	0
2	**53-OTf**	0	6
3	**54-BF_4**	0	0
4	**55**	0	0

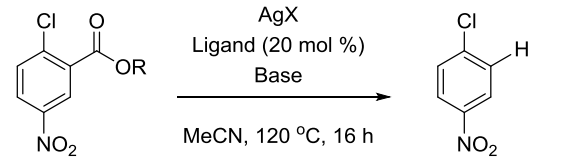
[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of **Ag-17** and 1.5 equiv of the stated F^+ source using 0.5 mL anhydrous DMSO in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR analysis using *p*-xylene as an internal standard. [c]Remaining mass balance is unreacted starting material.

Fluorinations employing F^+ sources are commonly carried out in acetone, MeCN, alcoholic, apolar aromatic or chlorinated solvents; however, there are scant examples of reactions in DMSO and none above ambient temperature.[221] Before further optimisation of the fluorodecarboxylation was attempted, a stability study of F^+ sources in DMSO was carried out (see supporting information, S3.1.). On dissolving **55** in DMSO at room temperature a vigorous exothermic reaction was observed, although there was no discernible physical reaction with DMSO and **51**, **53-OTf** or **54-BF_4** at ambient temperature, when these reagents were heated to 100 °C for 16 h in an MeCN:DMSO (95:5) solvent mixture, significant decomposition was observed. In every case, less than 5% of the unchanged F^+ starting material was detected following reaction. Heating the pyridinium reagents **53-OTf** and **54-BF_4** in the DMSO mixture for 16 h resulted in 37% and 8% fluorine incorporation in another part of the molecule. However, the remaining fluorine mass balance for all reagents following decomposition could not be accounted for. No fluoride was observed by ^{19}F NMR and no fluorine peak could be attributed to the fluorinated decomposition product, however it is possible that the chemical shift was outside of the sweep-width of the spectrometer.

To ensure that subsequent fluorodecarboxylation attempts were not being hampered by an unknown reactive fluorinated species formed on reaction with DMSO, the solvent system was switched to MeCN. But first the effectiveness of MeCN in promoting decarboxylation was assessed, using the protodecarboxylation reaction as a control (Table 12). Using MeCN as the reaction solvent with 10 mol % Ag_2CO_3 only afforded 14% protodecarboxylation in the absence of an additional ligand (Table 12, entry 1). The addition of the sulfoxide ligand 1,2-bis(phenylsulfinyl)ethane (**82**) gave no improvement on yield (Table 12, entry 2), and the use of the bis-phenenathroline silver complex

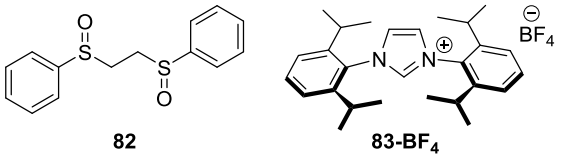
$Ag(Phen)_2OTf$ gave poor conversion of the potassium carboxylate **K-17** (Table 12, entry 3). Next the addition of the IPr NHC salt **83-BF_4** was investigated (Table 12, entries 4-6). A slight improvement in yield was achieved using **83-BF_4** and the acid (**17**) with Ag_2CO_3 as the silver salt or starting from the carboxylate (**K-17**) in conjunction with AgOAc (Table 12, entries 4 and 5, respectively). However, with the addition of 30 mol % K_2CO_3, 55% conversion to the protodecarboxylated product **17a** could be obtained (Table 12, entry 6); presumably the additional base helps promote formation of the Ag-NHC complex *in situ*. With these promising results in hand, the next step was to test these conditions in conjunction with an F^+ source (Table 13).

Table 12. Investigating the protodecarboxylation of **17** and **K-17** in MeCN wth the addition of ligands[a]



R = H; **17**
R = K; **K-17**

17a



82 **83-BF_4**

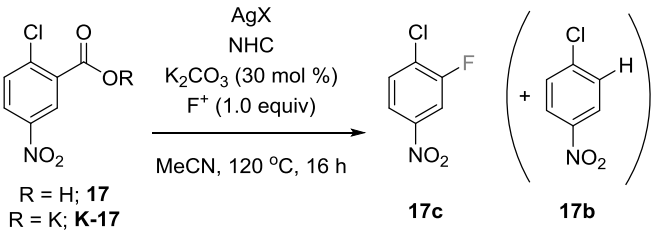
Entry	Substrate	AgX (mol %)	Base	Ligand	Yield[b] H (%)
1	**17**	Ag_2CO_3 (10 mol %)	-	-	14
2	**17**	Ag_2CO_3 (10 mol %)	-	**82**	10
3	**K-17**	$Ag(phen)_2OTf$ (20 mol %)	-	-	3
4	**K-17**	AgOAc (20 mol %)	-	**83-BF_4**	25
5	**17**	Ag_2CO_3 (10 mol %)	-	**83-BF_4**	20
6	**17**	Ag_2CO_3 (10 mol %)	K_2CO_3 (30 mol %)	**83-BF_4**	55

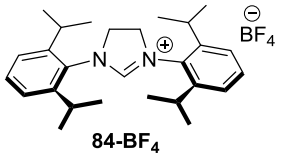
[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of substrate and the stated amounts of Ag source, ligand and K_2CO_3 using 0.5 mL anhydrous MeCN in a 10 mL sealed vial. [b]Yields determined by ^1H NMR analysis using *p*-xylene as an internal standard. [c]Remaining mass balance is unreacted starting material.

The optimised conditions for the Ag/IPr decarboxylation were tested with a number of different sources of electrophilic fluorine (Table 13, entries 1-3). Unfortunately none of the desired fluoroarene product was observed, in addition a small amount of conversion to the protodecarboxylation by-product occurred with no detection of an aryl-Ag(IPr) intermediate. Another NHC ligand source SIPr.HBF_4 (**84-BF_4**) was tested, with similar results (Table 13, entries 4-5). Finally the reaction was carried out with the potassium carboxylate starting material (**K-17**) and a stoichiometric amount of Ag and ligand and 30 mol % K_2CO_3, with no trace of fluorinated product and poor conversion to the protodecarboxylated product again observed (Table 13, entry 6). The

reaction was also repeated in the absence of base in the event that this may have a deleterious effect on **55**, but similarly disappointing results were observed (Table 13, entry 7).

Table 13. Attempted fluorodecarboxylation of **17** and **K-17** in MeCN using an Ag/NHC ligand system[a]





Entry	Substrate	AgX (mol %)	NHC (mol %)	F+	Product distribution[b]	
					H (%)	F (%)
1	**17**	Ag_2CO_3 (10)	**83-BF$_4$** (20)	**51**	9	0
2	**17**	Ag_2CO_3 (10)	**83-BF$_4$** (20)	**54-OTf**	1	0
3	**17**	Ag_2CO_3 (10)	**83-BF$_4$** (20)	**55**	4	0
4	**17**	Ag_2CO_3 (10)	**84-BF$_4$** (20)	**51**	4	0
5	**17**	Ag_2CO_3 (10)	**84-BF$_4$** (20)	**55**	8	0
6	**K-17**	AgOAc (100)	**83-BF$_4$** (100)	**55**	10	0
7[c]	**K-17**	AgOAc (100)	**83-BF$_4$** (100)	**55**	5	0

[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of substrate and the stated amounts of AgX, ligand, K_2CO_3 and F^+ source using 0.5 mL anhydrous MeCN in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR analysis using *p*-xylene as an internal standard. [c]Without K_2CO_3

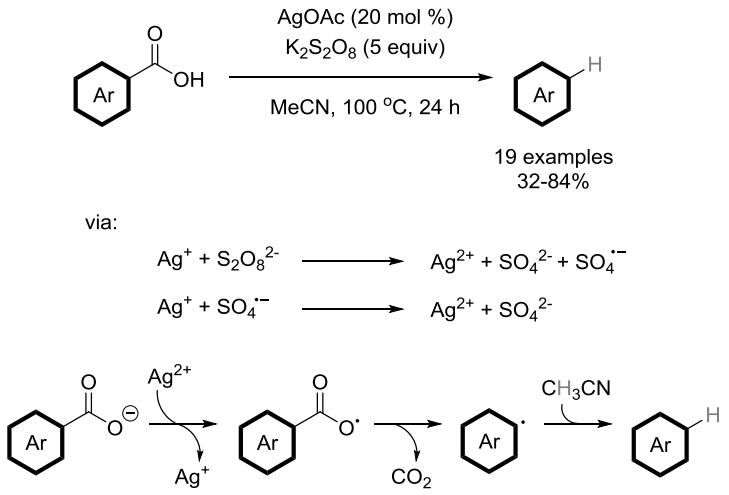
3.4.3. Conclusions

After several attempts it seems that fluorodecarboxylation cannot be induced using this Ag-catalysed approach in the presence of F^+ sources. Despite optimising the protodecarboxylation in a different solvent which does not react with electrophilic fluorine sources (MeCN) and using an NHC ligand to stabilise Ag, no trace of the fluorinated product could be observed in any case. Moreover, the addition of F^+ in the reaction media appears to have a detrimental effect on decarboxylation which can be delineated from two key sets of experiments, listed in Table 11 and 13. When the silver carboxylate (**Ag-17**) was synthesised and reacted in the presence of four different electrophilic fluorinating reagents and DMSO, no conversion was observed even to the protodecarboxylation by-product. To rule out the presence of a reactive fluorine-containing species (formed through a decomposition pathway with DMSO) preventing decarboxylation from the Ag-carboxylate, the reaction was optimised in MeCN, a solvent more commonly used with F^+ reagents (Table 12). Even with stoichiometric amounts of Ag and a ligand, poor conversion was again observed. Electrophilic

fluorine sources are highly oxidising, and Selectfluor (for example) has been theorised to oxidise Ag(I) salts to Ag(III).[218] Although Greaney *et al.*[27] have shown that Ag(II) can promote the decarboxylation of benzoic acids, perhaps Ag(III) cannot, thus explaining the poor conversion observed when Ag salts were used in conjunction with F^+ sources.

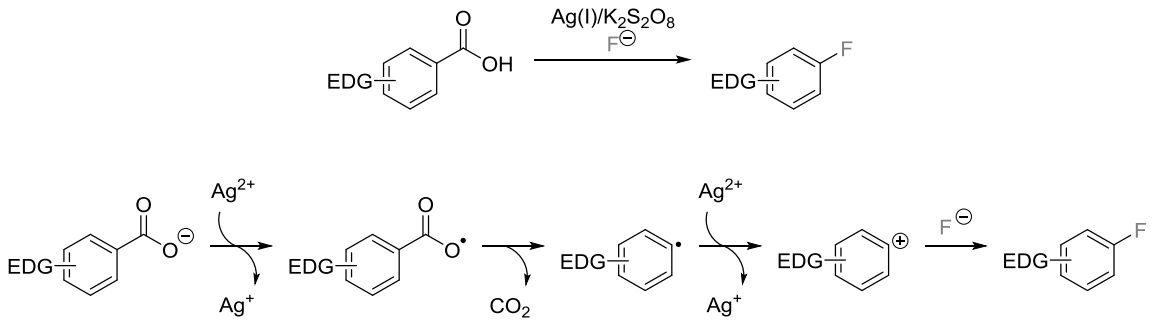
3.4.4. Aims of the project – Fluorination via a Ag(II) decarboxylation route

As previously discussed in Chapter 1 (Scheme 12), Greaney and co-workers have recently shown that benzoic acids can be utilised to form new C–H or C–C bonds via decarboxylative activation. This reaction is thought to proceed via a Ag(II) catalysed radical pathway (Scheme 12).



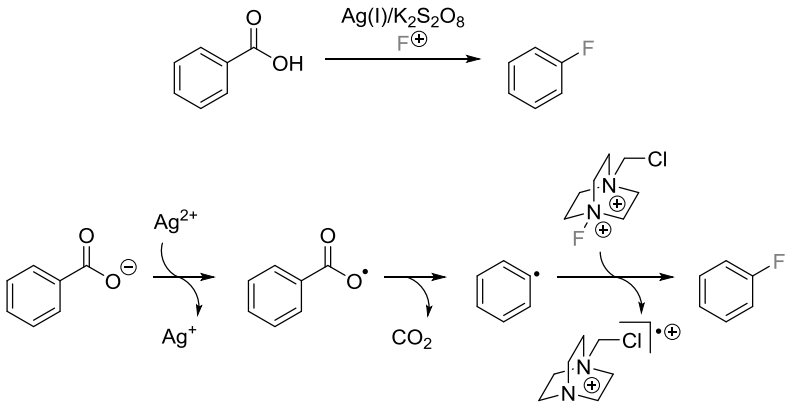
Scheme 12. The Ag-catalysed protodecarboxylation of benzoic acids reported by Greaney *et al.* occurs via a radical pathway.[27a]

Using this approach, in conjunction with electron-rich substrates it may be possible to oxidise the aryl-radical intermediate to a carbocation which could subsequently react with a fluoride source in a C–F bond forming step (Scheme 102).



Scheme 102. Proposed Ag(II)-catalysed fluorination of a cationic intermediate.

Alternatively, Selectfluor (and other sources of F^+) have been shown to act as radical fluorine donors.[210,214,215,216] Recently Tang *et al*. have shown that using a combined $Ag/S_2O_8^{2-}$/Selectfluor system, benzylic C-H fluorination can be achieved.[213] The reaction is thought to proceed via generation of Ag(II) which can facilitate abstraction of a benzylic C−H to form a radical which subsequently reacts with Selectfluor in the product forming step (Scheme 97). Although we have previously observed that aromatic decarboxylation is not facilitated under reaction conditions which are thought to generate Ag(III). The oxidation of Ag(I) to Ag(II) by $K_2S_2O_8$ may occur faster than the oxidation of Ag(I) to Ag(III) by Selectfluor, thus allowing radical decarboxylation to occur in a manner similar to that reported by Greaney *et al.*[27] Once the phenyl radical has been generated it could then react with Selectfluor forming an aryl−F bond, generating an aminium radical which could subsequently reoxidise Ag(I) to Ag(II) (Scheme 103), in a similar manner to reaction mechanism proposed by Tang *et al.*[213]

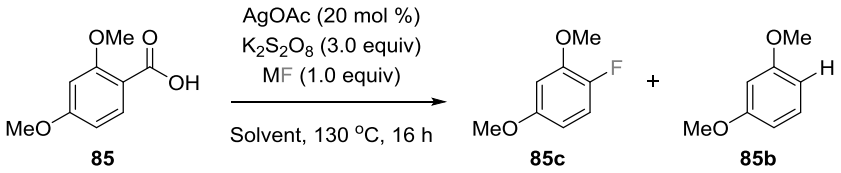


Scheme 103. Proposed Ag(II)-catalysed fluorination of a radical intermediate.

3.4.6. Exploratory experiments

To assess the feasibility of the reaction proposed in Scheme 102, the electron-rich 2,4-dimethoxy benzoic acid (**85**) was tested under a number of reaction conditions, summarised in Table 14. The reaction conditions initially reported by Greaney *et al.*[27a] were employed with the addition of metal fluoride salts (Table 14, entries 1-2); in these reactions no trace of the desired product was formed with the only observed products arising through coupling with the solvent, a similar product distribution occurred without the addition of the metal fluoride salt (Table 14, entry 3). Other solvents were tested in an attempt to limit solvent related by-products (Table 14, entries 4-8), however no fluorinated product was observed and the only products observed again arose from reaction with solvent of small amounts of **85b** from hydrogen abstraction.

Table 14. Attempted fluorodecarboxylation of **85** via generation of a cationic intermediate[a]

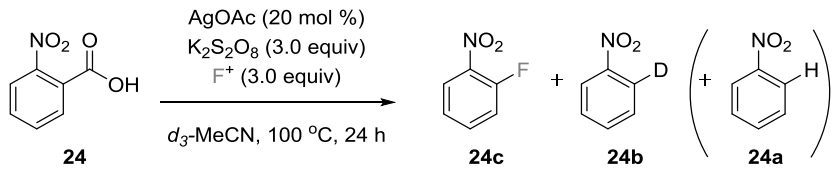


Entry	MF	Solvent	Product distribution (%)[b]		
			F	H	By-products
1	AgF	MeCN	0	0	29
2	KF	MeCN	0	0	35
3	-	MeCN	0	0	30
4	KF	DMF	0	10	5
5	KF	Propylene carbonate	0	3	39
6	KF	MeOH	0	3	61
7	KF	Toluene	0	trace	17
8	KF	DCE	0	0	17

[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of **85**, 20 mol % AgOAc, 3.0 equiv $K_2S_2O_8$ and 1.0 equiv of MF using 0.5 mL anhydrous solvent in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR analysis using mesitylene as an internal standard.

Next, conditions for the second proposed decarboxylative fluorination reaction (outlined in Scheme 103), were tested. Greaney and co-workers have reported that under Ag(II) decarboxylation conditions, the protodecarboxylation by-product could be supressed using a deuterated solvent,[27b] in view of this, preliminary reaction conditions were screened using 2-nitrobenzoic acid **24**, Ag(I)/$K_2S_2O_8$ in d_3-MeCN in the presence of three different electrophilic fluorinating reagents (Table 15).

Table 15. Attempted fluorodecarboxylation of **24** via generation of a radical intermediate[a]



Entry	F^+	Product distribution (%)[b]		
		F	D	By-products
1	**56**	0	0	22
2	**54-OTf**	0	21 (**24a**)	0
3	**51**		complex mixture	

[a]Reaction conditions: all the reactions were carried out under N_2 atmosphere with 0.1 mmol of **24**, 20 mol % AgOAc, 3.0 equiv $K_2S_2O_8$ and 3.0 equiv of the stated F^+ source using 0.5 mL d_3-MeCN in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR analysis using mesitylene as an internal standard.

In each attempt no trace of the desired fluorinated product **24c** was observed. Reaction with Selectfluor II (**56**) gave 22% of a by-product which appeared to arise through coupling with the solvent, in a similar manner to the experiments outlined in Table 14. Reaction with the *N*-fluoropyridinium reagent **54-OTf** gave 21% of the proto- not deutero-decarboxylation product which may be an expected by-product when using a deuterated solvent, however **24a** may arise through hydrogen abstraction from a methyl group on the 2,4,6- pyridinium of **54-OTf**. Finally, reaction with the *N*-fluorosulfonamide reagent **51** resulted in a complex mixture.

3.4.7. Conclusions

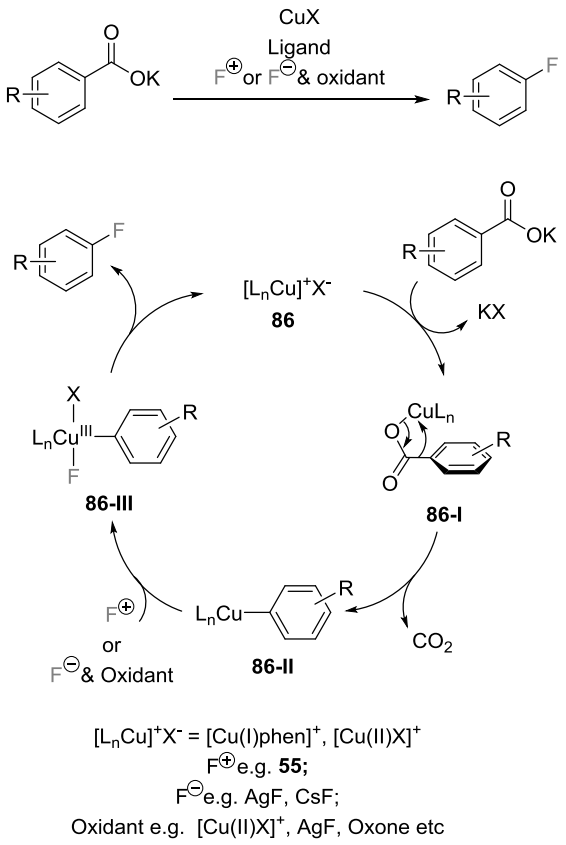
Although the exploratory experiments in Tables 14 and 15 gave no trace of the desired fluorinated product, they do not necessarily indicate that the proposed ideas outlined in Schemes 102 and 103 will not work. Subsequent optimisation could be carried out by initially screening other substrates and reaction temperatures; however the observation of no trace of product in these preliminary experiments caused us to explore other avenues to facilitate decarboxylative aromatic fluorination.

3.4.8. Aims of the project – Fluorination via a Cu decarboxylation route[xii]

The ability of copper complexes to facilitate decarboxylation is well known and can occur in the presence of Cu(I) or Cu(II) salts and an appropriate ligand (e.g. phenanthroline) or a polar coordinating solvent; these transformations were discussed in depth in Chapter 1. The recent reports of Cu-mediated fluorination in the presence of nucleophilic or electrophilic fluorine sources (discussed in Section 3.2.4.), led us to postulate the likelihood of a Cu-catalysed decarboxylative fluorination mechanism (Scheme 104).

In line with previous reports,[182,185,186] the proposed mechanism shown in Scheme 104 could occur through several manifolds. In the presence of Cu(I) salts, decarboxylation could occur generating an aryl-Cu(I) complex (**42-II**) which could then be oxidised to a Cu(III)-fluoride (**42-III**) either by an F^+ source, two molecules of AgF, or Cu(II)-F generated from Cu(I) and AgF. Alternatively the Cu(III)-fluoride may also be accessed by a stepwise ligand exchange then oxidation. In the presence of Cu(II) salts decarboxylation would generate an aryl-Cu(II) complex (**42-II**) which could then undergo ligand exchange and oxidation using AgF or again in a stepwise manner via ligand exchange with a fluoride source then oxidation by another molecule of Cu(II). Once the Cu(III)-fluoride (**42-III**) is accessed, reductive elimination to form the aryl-fluoride product should be facile.[181,182,183]

[xii] This work was carried out jointly with Dr Francisco Juliá-Hernández, however all the reactions listed herein were carried out solely by the author.



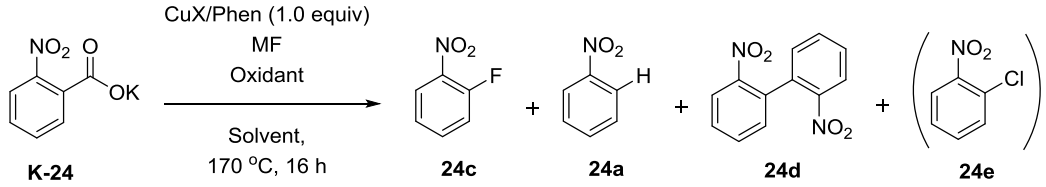
Scheme 104. Proposed Cu-catalysed decarboxylative fluorination methodology.

3.4.9. Optimisation attempts

To assess the feasibility of the proposed transformation in Scheme 104, several different reaction conditions were screened using both Cu(I) and Cu(II) sources with different fluoride sources and the addition of Selectfluor as an oxidant (Table 16). To limit the formation of the protodecarboxylation by-product **24a**, the reaction conditions were screened using the potassium salt **K-24**, oven dried glassware and an Ar atmosphere; however in every case the by-product **24a** was observed in significant amounts (Table 16, entries 1-11). Using either CuI or $CuCl_2$ in combination with Selectfluor (**55**), 5.0 equiv of KF and different solvents (anisole or propylene carbonate) no fluorinated product or other products which may occur through reductive elimination from a Cu(III) intermediate were observed (e.g. **24d** or **24e**). In the absence of **55**, with 5.0 equiv of AgF and using anisole or $PhCF_3$ as the solvent, no fluorinated product was again observed (Table 16, entries 5-10). However, in these reactions significant amounts of homocoupling (**24d**) were detected by ^{1}H NMR and GC-MS analysis, indicating that a Cu(III) intermediate may be generated in the reaction conditions.[181] Finally, when the reaction solvent was changed to toluene and the loading of AgF decreased to 2.5 equiv, trace amounts of the fluorinated product **24c** were observed by ^{19}F NMR and GC-MS, however the amount

was so low that it could not be observed by ^{1}H NMR (Table 16, entry 11). In addition the homocoupling (**24d**) and chlorinated product (**24e**) were also observed in 28% and 3%, respectively.

Table 16. Attempted fluorodecarboxylation of using Cu-catalysis[a]



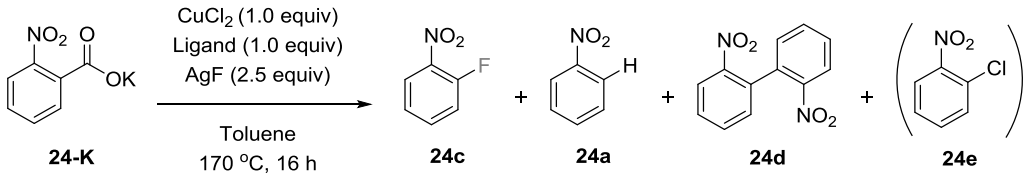
K-24 **24c** **24a** **24d** **24e**

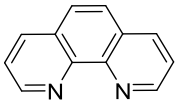
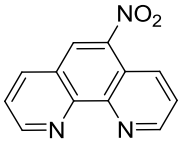
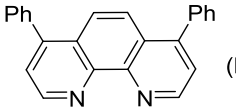
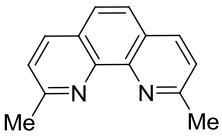
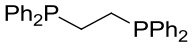
Entry	CuX	MF (equiv)	Oxidant (equiv)	Solvent	Product distribution (%)[b]			
					24c Ar-F	**24a** Ar-H	**24d** Ar-Ar	**24e** Ar-Cl
1	$CuCl_2$	KF (5.0)	**10** (1.5)	Anisole	0	5	0	0
2	CuI	KF (5.0)	**10** (1.5)	Anisole	0	15	0	-
3	$CuCl_2$	KF (5.0)	**10** (1.5)	Propylene carbonate	0	18	0	0
4	CuI	KF (5.0)	**10** (1.5)	Propylene carbonate	0	23	0	-
5	$CuCl_2$	AgF (5.0)	-	Anisole	0	58	20	0
6	CuI	AgF (5.0)	-	Anisole	0	15	4	-
7	$CuCl_2$	AgF (5.0)	-	$PhCF_3$	0	33	38	0
8	CuI	AgF (5.0)	-	$PhCF_3$	0	39	38	-
9	$CuCl_2$	AgF (5.0)	-	$PhCF_3$	0	30	40	0
10	CuI	AgF (5.0)	-	$PhCF_3$	0	54	26	-
11	$CuCl_2$	AgF (2.5)	-	Toluene	trace	27	28	3

[a]Reaction conditions: all reactions were carried out in oven-dried glassware under Ar atmosphere. 0.1 mmol **K-24**, and the stated reagents were heated to 170 °C for 16 h, in a 10 mL sealed vial using 0.5 mL of the stated solvent. [b] Yields calculated using mesitylene as an internal standard.

Using the conditions in Table 16 which gave trace amounts of product (entry 11), the nature of the ligand was investigated (Table 17). When the reaction was repeated with phenanthroline (entry 1) trace amounts of product were again observed, but with an increased amount of protodecarboxylation and homocoupling (**24a** and **24d**). Using 5-nitro phenanthroline or bathophenanthroline (BPhen), trace amounts of **24c** and increased amounts of the chlorination by-product (**24e**) were detected (Table 17, entries 2 and 3, respectively). No fluorination product was observed with 2,9-dimethylphenanthroline, 1,2-bis(diphenylphosphino)ethane, SIPr.HCl (**84-Cl**) or SIPr.BF_4 (**84-BF_4**) (Table 17, entries 4-7).

Table 17. Screening of the ligand system[a]



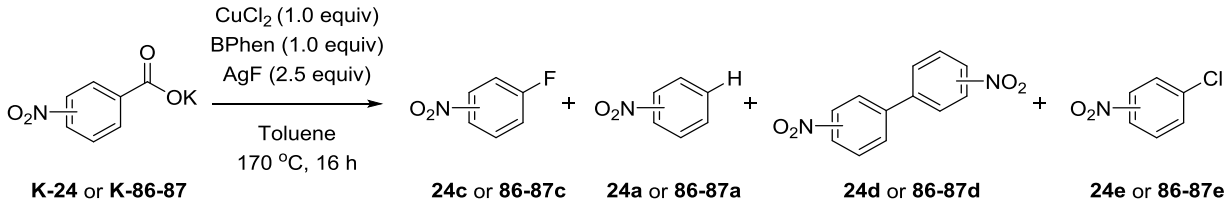
Entry	Ligand	Product distribution (%)[b] 24c Ar-F	24a Ar-H	24d Ar-Ar	24e Ar-Cl
1	 (Phen)	trace	42	46	2
2		trace	18	28	5
3	 (BPhen)	trace	16	55	18
4		0	40	22	4
5		0	40	6	4
6	SIPr.HCl (**84-Cl**)[c]	0	38	trace	4
7	SIPr.HBF_4 (**84-BF_4**)[c]	0	83	0	-

[a]Reaction conditions: all reactions were carried out in oven-dried glassware under Ar atmosphere. 0.1 mmol **K-24**, and the stated reagents were heated to 170 °C for 16 h, in a 10 mL sealed vial using 0.5 mL of anhydrous toluene. [b] Yields calculated using mesitylene as an internal standard. [c]Reaction carried out with $CuCO_3$.CuOH instead of $CuCl_2$.

When the conditions shown in Table 17, entry 3 were tested with different nitro-benzoic acid isomers (**K-86** or **K-87**), unfortunately no trace of the desired fluorination products (**86c** or **87c**) were observed (Table 18, entries 2 and 3, respectively). Furthermore, poor conversion was realised with these substrates, resulting in the production of little or none of the other by-products. The reaction system ($CuCl_2$/phenanthroline ligand, toluene, 170 °C) was adapted from Patel and Mainolfi's system for the Cu-catalysed decarboxylative C−N coupling (Chapter 1, Scheme 6).[16] In this paper, all the

benzoic acid substrates are *ortho*-substituted, although Gooβen *et al.* have reported the high yielding decarboxylation of other *meta*- and *para*-nitro benzoic acid isomers, albeit with a different solvent system (NMP). [17] In this vein the reaction of all three nitrobenzoic acid isomers were tested using NMP as the solvent with AgF or CsF in combination with a variety of oxidants, however no trace of the fluorinated product was observed.

Table 18. Screening of the substrate[a]



K-24 or **K-86-87** **24c** or **86-87c** **24a** or **86-87a** **24d** or **86-87d** **24e** or **86-87e**

Entry	Substrate	Product distribution[b]			
		Ar-F	Ar-H	Ar-Ar	Ar-Cl
1	2-nitro (**K-24**)	Trace	14%	57%	13%
2	3-nitro (**K-86**)	0%	6%	0%	Trace
3	4-nitro (**K-87**)	0%	3%	Trace	3%

[a]Reaction conditions: all reactions were carried out in oven-dried glassware under Ar atmosphere. 0.1 mmol substrate, and the stated reagents were heated to 170 °C for 16 h, in a 10 mL sealed vial using 0.5 mL of anhydrous toluene. [b]Yields calculated using mesitylene as an internal standard.

3.4.10. Conclusions

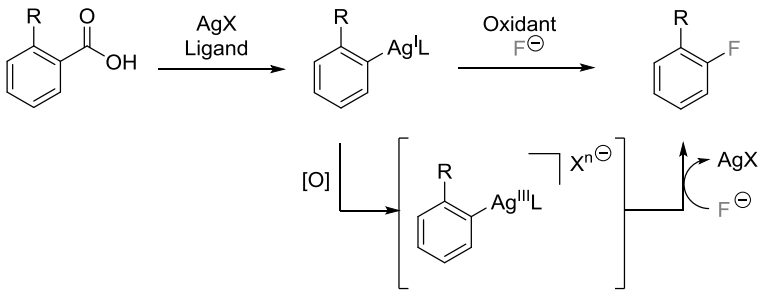
After testing a wide variety of conditions only trace amounts of product arising from Cu-catalysed decarboxylative fluorination were observed using 1 equiv of $CuCl_2$ and potassium 2-nitrobenzoate. On testing other substrates (including potassium *meta*- and *para*-nitrobenzoates and potassium 2-chloro-5-nitrobenzoate[xiii]) no trace of the desired fluorination products were ever observed. The observation of chlorination and homocoupling by-products indicate the formation of a Cu(III) intermediate. Reductive elimination from a Cu(III)-fluoride is reported to be facile[181,182,183] and has been reported to occur at room temperature[185] however the Cu(III)-fluoride generated in the reactions detailed in this section may be unstable at such high temperatures (170 °C), but unfortunately such elevated temperatures are required to facilitate decarboxylation in the presence of Cu.

[xiii] The reactions using potassium 2-chloro-5-nitrobenzoate were not discussed here, however no trace of fluorinated product was observed. Reaction with substrate resulted in a similar by-product distribution as potassium 2-nitrobenzoate in addition to S_NAr displacement of chlorine with fluoride.

3.4.11. Overall conclusions and future outlook

In this chapter the decarboxylative fluorination of benzoic acids was investigated using a number of different metal-catalysed systems. Using Ag(I) salts, the fluorinating reagents were found to be unstable in DMSO, the standard reaction solvent. As a consequence, the protodecarboxylation reaction was used as a control to optimise the decarboxylation in MeCN. Using an NHC ligand and base the protodecarboxylation was improved 4-fold (cf. Table 12, entries 1 and 6). Following this optimisation the reaction was carried out in the presence of F^+ sources, however no trace of the fluorination product was observed, even with a stoichiometric amounts of Ag and ligand (Table 13). In these reactions poor conversion was realised perhaps indicating that the Ag(I) catalyst was being oxidised to a Ag(III) compound which could not undergo decarboxylation.

Recently Ribas and co-workers have demonstrated the aromatic fluorination of an aryl-Ag(III) complex.[222] The reaction involves oxidative addition of a Ag(I) salt into an aryl-halide bond followed by nucleophilic substitution with fluoride. Formation of the aryl fluoride from the aryl-Ag(III) complex is slow, affording only 39% after 24 h reaction. However, TBAF.3H_2O was used as the fluoride source and it is a relatively poor source of nucleophilic fluorine and the reaction may be improved with an anhydrous F^- source or KF and a cryptand. If an aryl-Ag(I) intermediate can be generated via decarboxylation, then oxidised to Ag(III) with a suitable oxidant and ligand, the nucleophilic substitution with fluoride may be possible. The stability of the Ag(I)-NHC intermediate formed in the control protodecarboxylation reaction (Table 12, entry 6) is unknown, however if it can be generated in stoichiometric amounts, this would be a good starting point to investigate the fluorination using an oxidant and fluoride source. Although this approach may require stoichiometric amounts of Ag and ligand, if the substitution can occur rapidly in the presence of a competent source of nucleophilic fluoride it could offer a new route to [^{18}F] incorporation.

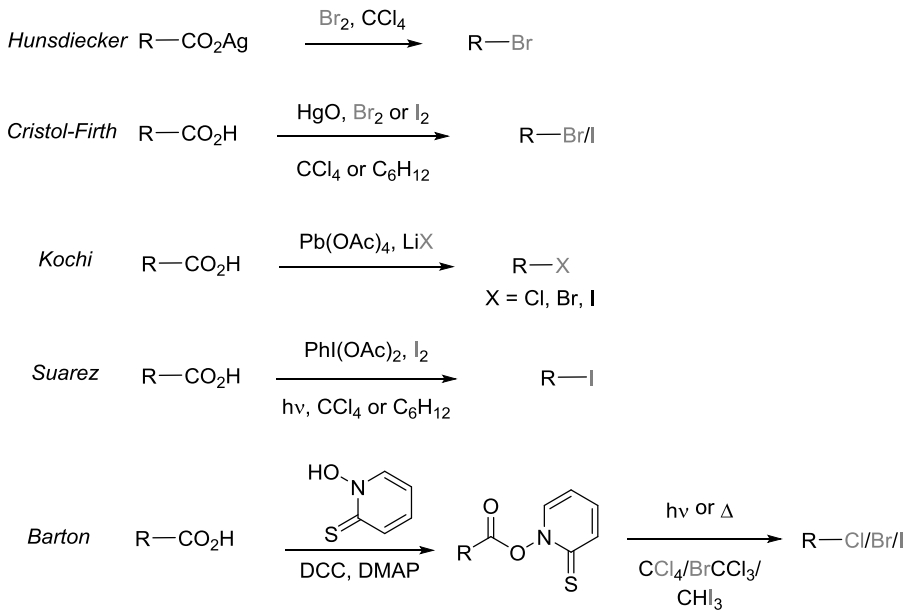


Scheme 105. Proposed nucleophilic fluorination of an aryl-Ag(III) intermediate

During the investigation of the Cu catalysed decarboxylative fluorination methodology, several conditions were tested but only trace amounts of product were observed with only one substrate (potassium 2-nitrobenzoate). The reaction conditions required for Cu-catalysed decarboxylation (170 ^{o}C) may have been too high to generate the desired aryl-Cu(III) fluoride complex in an appreciable amount. Further investigation into this transformation could be carried out using cooperative Ag catalysis, whereby the decarboxylation could be facilitated by Ag at lower temperatures, then undergo transmetallation to Cu,[29,30] followed by fluoride transfer and oxidation, then reductive elimination in an analogous manner to the original proposal (Scheme 104).

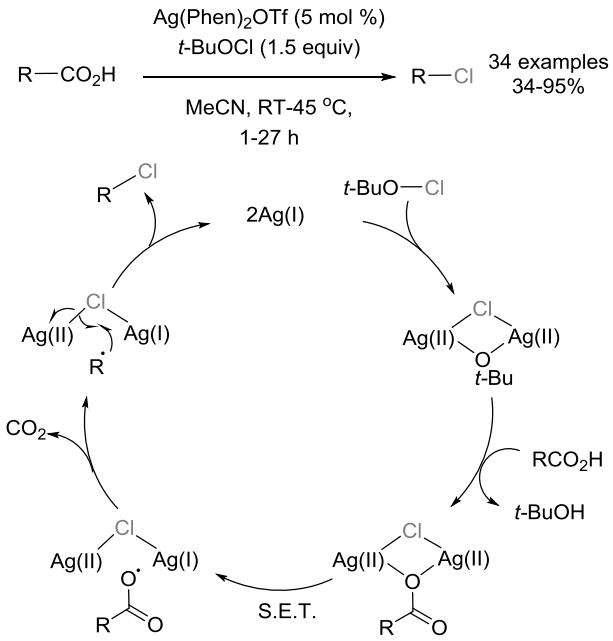
3.5. DECARBOXYLATIVE FLUORINATION – ALKYL FLUORIDE FORMATION

3.5.1. Aims of the project



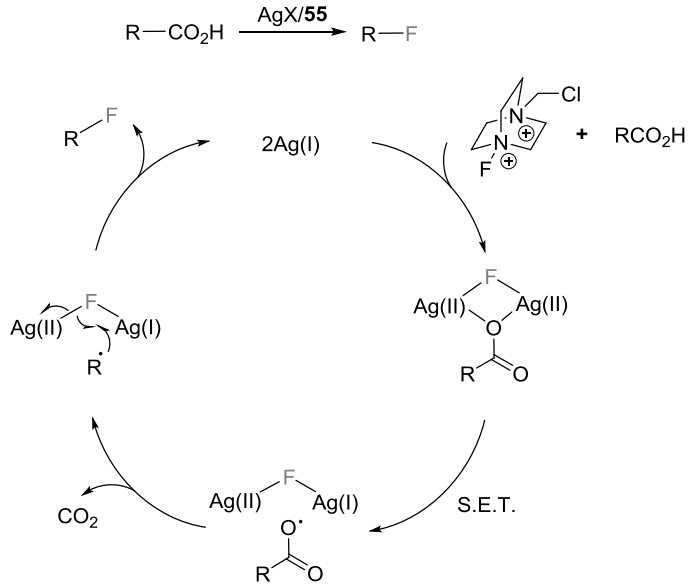
Scheme 106. Traditional decarboxylative halogenation methodologies involving radical intermediates.

The first example of a decarboxylative halogenation reaction was discovered in 1861 by Alexander Borodin and subsequently patented by Cläre and Heinz Hunsdiecker in 1940 (Scheme 106).[217] These early methodologies required the use of stringently dried silver carboxylates and corrosive or toxic reagents (Br_2 and CCl_4). Due to the limitations of these initial works, a number of modifications have been developed. Cristol and Firth, and Kochi reported the decarboxylative halogenation of carboxylic acids using mercury and lead salts.[223] Although these approaches did not require the pre-formation of the metal carboxylate, the toxicity of these metal salts makes their use in synthesis highly undesirable. Later, Suarez and Barton developed metal-free procedures using stoichiometric amounts of organic compounds to generate carboxy radicals.[224] It was not until 2012 the first catalytic Hunsdiecker-type reaction was reported. Using Ag-catalysis and *t*-BuOCl as the oxidant and chlorine source the Li group were able to chlorodecarboxylate a wide variety of primary (1^o), secondary (2^o) and tertiary (3^o) aliphatic acids at ambient temperature (Scheme 107).[218]



Scheme 107. The Ag-catalysed decarboxylative chlorination reported by Li *et al.* is the first example of a catalytic Hunsdiecker-type reaction.[218]

Inspired by this discovery and in line with our previous goal to develop a decarboxylative fluorination methodology it seemed reasonable that this protocol could be modified using Selectfluor as the oxidant and fluorine source (Scheme 108).

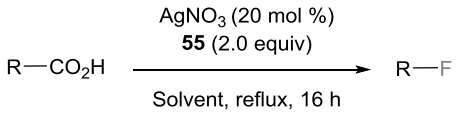


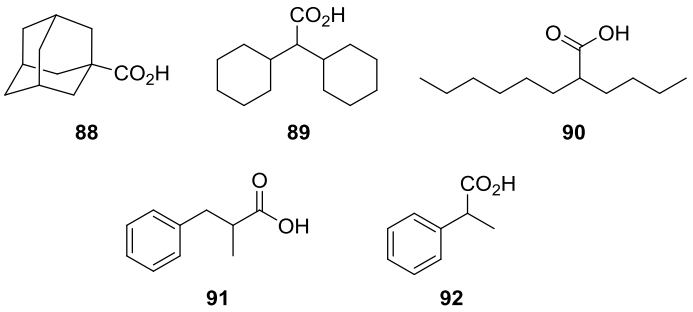
Scheme 108. Proposed Ag-catalysed decarboxylation using Selectfluor as the oxidant and fluoride source.

3.5.2. Optimisation

Initially the reaction conditions were explored using 1-adamantane carboxylic acid **88**, the optimisation substrate used by Li *et al.* in their chlorination paper.[218] However, after several attempts with differing loadings of Ag/Phen, different F^+ sources, different solvents and even lowering the reaction temp to 0 °C and using short reaction times of 10 mins, it was not possible to obtain the mono-fluorinated product in high yield and with good regioselectivity. This substrate was deemed too reactive so **89** was tested with Ag/Phen and **55** in MeCN and only afforded 2% conversion in 1 hour at 30 °C.

Table 19. Investigating the Ag-catalysed decarboxylative fluorination conditions reported by Li *et al*.[a]





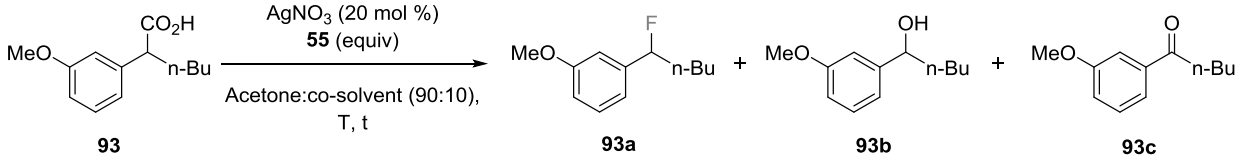
Entry	Substrate	Solvent	Product distribution[b]		
			Conversion	F	Other
1	**90**	H_2O	trace	0	
2	**90**	H_2O:Acetone (1:1)	0	89	[c]
3	**91**	H_2O	1	9	[c]
4	**91**	H_2O:Acetone (1:1)	90	63	[c]
5[d]	**91**	H_2O:Acetone (1:1)	90	84	
6[e]	**91**	H_2O:Acetone (1:1)	86	83	
7[e]	**89**	H_2O:Acetone (1:1)	55	57	
8[e]	**92**	H_2O:Acetone (1:1)	>99	0	81% **OH**; 16% **C=O**

[a]Reaction conditions: all reactions were carried out under Ar atmosphere. 0.3 mmol substrate, and the stated reagents were heated to reflux for 16 h, in a 10 mL RBF with reflux condenser in the stated solvent mixture (0.12 M). [b]Yields calculated using mesitylene as an internal standard. [c]Remaining mass consists of several unidentifiable by-products. [d]Schlenk conditions. [e]Degassed solvent

During the optimisation of the reaction the Li group published an analogous decarboxylative fluorination methodology using $AgNO_3$ and Selectfluor under aqueous conditions (*vide infra*, Section 3.5.4).[219] When we tested a number of substrates using these conditions it was found that an H_2O:Acetone (1:1) mixture was best for the substrates tested (**89-92**) and by-product formation

could be suppressed with the use of degassed solvent and Schlenk conditions (Table 19, comparing entries 4-6). An intriguing observation occurred when substrate **92** was subjected to the reaction conditions. This acid gave no detected fluorinated product; instead the major products were the alcohol and the over-oxidation ketone product (Table 19, entry 8). In their paper, Li *et al.* had no examples of substrates bearing the carboxylic acid in the benzylic position so we decided to further investigate this transformation.[219]

Table 20. Investigating the reaction of **93** using $AgNO_3$ and **55**[a]



93 **93a** **93b** **93c**

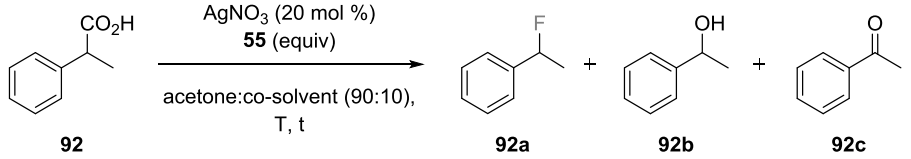
Entry	**55** (equiv)	Co-solvent	T (^{o}C)	t (h)	Product distribution (%)[b,c]			
					Conversion	F	OH	C=O
1	1.50	H_2O	80	16	>99	0	77	13
2	1.50	H_2O	80	1	>99	27	46	11
3	1.25	H_2O	70	1	>99	71	0	7
4	1.15	H_2O	70	1	>99	73	2	2
5	1.10	H_2O	70	1	>99	70	2	2
6	1.15	EtOH	70	1	0	0	0	0
7	1.15	Propylene carbonate	70	1	0	0	0	0
8	1.15	2,2,2-TFE	70	1	0	0	0	0
9	1.15	HFIP	70	1	0	0	0	0
10	1.15	$MeNO_2$	70	1	0	0	0	0
11	1.15	MeCN	70	1	0	0	0	0
12	1.15	Diglyme	70	1	0	0	0	0
13	1.15	DME	70	1	0	0	0	0
14	1.15	AcOH	70	1	0	0	0	0

[a]Reaction conditions: all reactions were carried out under air atmosphere with 0.3 mmol **93**, 20 mol % $AgNO_3$ and the stated amount of **55** in a 10 mL sealed vial using the stated solvent (0.12 M). [b]Yields calculated using mesitylene as an internal standard. [c]Remaining mass balance comprises several unidentifiable byproducts.

The reaction was investigated using a benzyl carboxylic acid of higher molecular weight to limit any product volatility issues (**93**), and a 90:10 v/v acetone:H_2O solvent system (Table 20). Initially when **93** was heated to 80 ^{o}C for 16 h in the presence of 20 mol % $AgNO_3$ and 1.5 equiv of **55**, a similar observation to **92** occurred where none of the fluorinated product (**93a**) was detected, instead large amounts of alcoholic compounds were produced (Table 20, entry 1). When the reaction was repeated but stopped after 1 h, 27% fluoride was observed with a concomitant reduction in oxygen containing products (Table 20, entry 2). This reaction could indicate that the fluoride is an intermediate product *en route* to the alcohol (and subsequently the ketone). The reaction could be further optimised to favour formation of the fluoride with high regioselectivity

(Table 20, entry 3) by lowering the temperature (70 °C) and loading of **55** (1.15 equiv). The formation of the alcohol may result by reaction of the fluoride with water in the reaction media, and as a consequence the reaction was carried out in the presence of a variety of different polar co-solvents in place of H_2O (Table 20, entries 6-14). However, in every case no conversion was observed.

Table 21. Investigating the reaction of **92** using $AgNO_3$ and **55**[a]



Entry	**55** (equiv)	Co-solvent	T (°C)	t	Product distribution (%)[b,c]			
					Conversion	F	OH	C=O
1	1.5	H_2O	80	16 h	>99	0	76	15
2	1.5	H_2O	80	1 h	96	27	46	11
3	1.15	H_2O	70	30 min	91	29	6	38
4	1.15	H_2O	70	20 min	84	50	8	20
5	1.15	H_2O	80	20 min	>99	55	25	9
6	1.15	H_2O	80	15 min	>99	71	18	8
7	1.15	H_2O	90	15 min	>99	61	25	7
8	1.15	H_2O	90	5 min	<99	80	12	5
9	1.15	H_2O	90	2 min	<99	78	10	5
10	1.15	H_2O	90	1 min	41	34	4	3
11[d]	1.15	H_2O	90	10 min	12	6	0	2
12[e]	1.15	H_2O	90	10 min	trace	trace	0	0
13[f]	1.15	H_2O	90	10 min	0	0	0	0
14[f]	1.15	-	90	30 min	0	0	0	0
15[f,g]	1.15	-	90	30 min	0	0	0	0
16[f,g]	1.15	HFIP	90	30 min	0	0	0	0
17[f,g,h]	1.15	-	90	30 min	0	0	0	0

[a]Reaction conditions: all reactions were carried out under air atmosphere with 0.3 mmol **92**, 20 mol % $AgNO_3$ and the stated amount of **55** in a 10 mL sealed vial using the stated solvent (0.12 M). [b]Yields calculated using mesitylene as an internal standard. [c]Remaining mass balance comprises several unidentifiable byproducts. [d]*t*-AmOH instead of Acetone. [e]*t*-BuOMe instead of Acetone. [f]MeCN instead of Acetone. [g]$AgBF_4$ instead of $AgNO_3$. [h]10% non-coordinating salt added e.g. NH_4SiF_6, NH_4PF_6, $NaSbF_6$, $LiNTf_2$, $NaBPh_4$, NH_4AlF_6.

Next the reaction conditions with **92** were investigated (Table 21). This acid had a different reactivity to **93**. The optimal reactions conditions for **93** were found to be heating to 70 °C for 1 h (Table 20, entry 4), however, when **92** was heated to 70 °C for 30 min excellent conversion occurred but only 29% of the fluoride was observed with the ketone being the major product, in addition to several unidentifiable by-products (Table 21, entry 3). Furthermore, stopping the reaction after 20 mins at this temperature gave only 50% fluoride and already 8% alcohol and 20% ketone (Table 21, entry 4). These observations could indicate that the decarboxylation is relatively slow at this temperature and large amounts of Selectfluor (**55**) or from a hypervalent Ag species are present in solution which could be consumed by oxidising any alcohol formed instead of facilitating

decarboxylation. Next the reaction temperature was increased to 80 °C and after 20 or 15 min reaction improved chemoselectivity for the fluoride occurred (Table 21, entries 5 and 6, respectively). The optimal reaction temperature was found to be 90 °C, and at this temperature quantitative conversion and high yields and chemoselectivity of the fluoride could be realised in as little as 2 mins, with 5 mins being the preferred reaction time (Table 21, entries 9 and 8, respectively).

The solvent effect was again investigated with this substrate. Previous optimisation with **93** (Table 20) indicated that the presence of water in the reaction media is important, with no product observed with acetone and different polar co-solvents. To investigate whether water is required to solubilise the silver source, Selectfluor or stabilise reactive intermediates, a number of alternatives were tested. $AgNO_3$ was replaced by $AgBF_4$ to improve solubility of the salt in MeCN. However, no conversion was observed even with addition of a per-fluorinated alcohol (Table 21, entries 15 and 16, respectively). To aid solubilisation of Selectfluor[225] a variety of weakly coordinating anion additives were tested in conjunction with $AgBF_4$ (Table 21, entry 17) but again no product was observed.

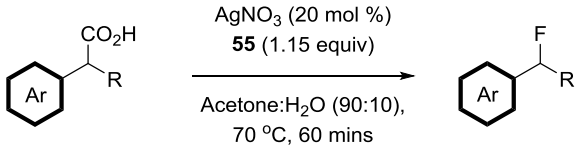
3.5.3. Substrate scope

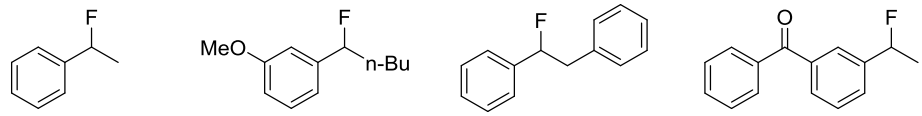
Once optimal conditions were established for two acids, the substrate scope was further investigated (Table 14). A number of different acids could be successfully reacted under the standard conditions (originally elucidated for **93**) without significant re-optimisation (Table 22, **94-95a** 70 °C 1 h; **98-99a** 70 °C, 30 mins). The reaction conditions were also amenable to scale up without a reduction in yield, with the reaction of **92** carried out on 5 mmol scale and **93** on 19 mmol scale. The reaction also tolerates a number of useful functional groups such as the ether (**93a**), ketone (**95a**), and iodo (**97a**) functionalities.

Whilst investigating the substrate scope, it quickly became apparent that benzylic fluorides suffer from stability issues. When pure, benzylic fluorides can rapidly decompose in the presence of catalytic amounts of strong acids or on borosilicate glass. This decomposition results in the production of HF and polymerisation products.[235] Due to their instability, they should not be stored neat on borosilicate glass but are stable in solution (e.g. acetone, MeCN, $CHCl_3$ (filtered through alumina), alkanes etc.) or stored over bases. Furthermore, final evaporations after column chromatography were carried out in a PFA round bottom flask (RBF); alternatively, the majority of the solvent can be removed in a borosilicate RBF then transferred to a soda-lime glass vial or plastic centrifuge tube for the final solvent removal. Considering the ever increasing number of procedures reported for the formation of benzylic fluorides,[205-207,209,211,213,215] and the documented instability of

these compounds,[235] the authors of these procedures rarely comment on the product instability or limiting the use borosilicate glassware for storing neat compounds.

Table 22. Substrate scope of the Ag-catalysed decarboxylative fluorination of benzyl carboxylic acids[a]



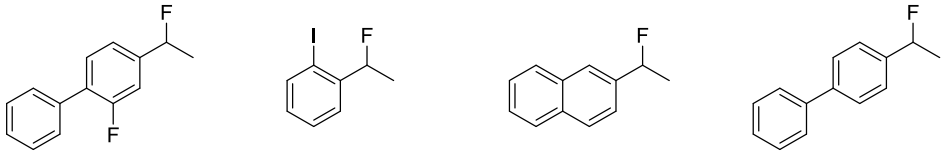


92a
(90%)[b,c] 84%
5 mins, *5 mmol scale*

93a
(71%)[b] 67%
19 mmol scale

94a
(83%)[b] 49%

95a
(88%)[b] 87%



96a
(75%)[b,d] 74%

97a
(74%)[b,c,e]
2 h

98a
(59%)[b] 52%
30 mins

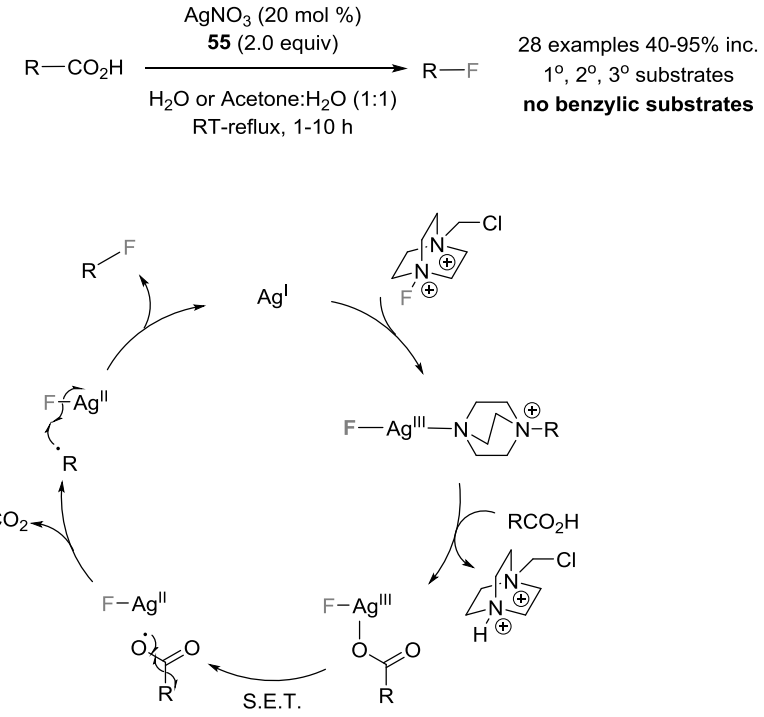
99a
(66%)[b]
30 mins

[a]Reaction conditions: unless otherwise stated all the reactions were carried under an air atmosphere with 1.0 equiv of acid, 20 mol % $AgNO_3$, 1.15 equiv of **55** at 70 °C for 60 min in a 10 mL sealed vial. Unless otherwise stated all yields correspond to the pure isolated product. [b]Yield was determined by ^1H NMR analysis using mesitylene or trimethoxybenzene as the internal standard. [c]Reaction carried out at 90 °C. [d]Reaction carried out at 50 °C. [e]Reaction carried out with 30 mol % $AgNO_3$.

3.5.4. Concurrent work by other research groups

As mentioned previously, during this project Li and co-workers published a Ag-catalysed decarboxylation methodology for the fluorination of a variety of aliphatic acids.[219] The reaction proposed mechanism shown in Scheme 48 involves initial oxidation of Ag(I) to Ag(III) by Selectfluor, the trivalent Ag(III)-fluoride complex then undergoes S.E.T. with a carboxylate ion, generating Ag(II)-F and a carboxy radical. Decarboxylation of the carboxy radical gives an alkyl radical which then reacts with the Ag(II) fluoride, forming the alkyl fluoride product and regenerating the Ag(I) catalyst. An alternative mechanism involving oxidation of the alkyl radical followed by fluoride capture was ruled out due to the poor nucleophilicity of F^- in the presence of water, and the requirement of aqueous conditions to facilitate reaction. A mechanism involving fluorine transfer from Selectfluor to an alkyl radical was also entertained, however a control experiment where 1-adamantecarboxylic acid was treated with a Ag(II) salt and Selectfluor only resulted in trace amounts of fluorinated

product with significant amounts of adamantan-1-ol observed. This indicates that the fluorine transfer from Selectfluor to the adamantane radical is slower than the oxidation, and that rapid fluorine transfer from a Ag(II)-fluoride likely occurs in the fluorination step.



Scheme 109. Ag-catalysed fluorodecarboxylation reported by Li *et al.*[219]

3.5.5. Conclusions and future outlook

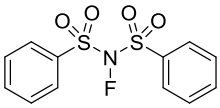
In conclusion, we have shown that benzylic fluorides can be generated via Ag-catalysed decarboxylation. The Ag-catalysed fluorination protocol reported by Li *et al.*[219] lacked any substrates bearing the carboxylic acid in the benzylic position, however through careful optimisation we have shown that these substrates can be fluorinated in very short reaction time. The rapid nature of the fluorination could be very useful for the radiolabelling of PET tracer molecules; however the instability of benzylic fluorides prevents their uses as motifs in medicinal chemistry.

Initially when the conditions reported by Li *et al.* were applied to a benzyl carboxylic acid substrate, we observed no formation of the fluoride product, instead conversion into the alcohol and ketone occurred. These initial experiments (Table 20 or 21, entries 1 and 2) indicate that the fluoride may react with water to form the alcohol product, as different regioselectivities were observed with 1 h and 16 h reaction. Due to the plethora of routes recently reported to synthesise benzylic fluorides, but the attributed instability of these compounds, a protocol which can use these activated substrates in new bond forming reactions would have great use as a new synthetic methodology. Accordingly, this topic is explored in the following chapter.

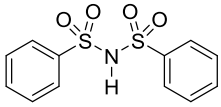
Chapter 3 – Supporting Information

S3.1. STABILITY EXPERIMENTS OF F^+ SOURCES IN DMSO

Table S3-1. Transformations of **51** in the presence of DMSO at ambient and high temperatures



51



51a

Entry	Solvent	Conditions	^{1}H NMR Yield		
			51	**51a**	**Other**
1	d_3-MeCN	RT	>99	0	<1
2	d_3-MeCN:d_6-DMSO (95:5)	RT	82	18	<1
3	d_3-MeCN:d_6-DMSO (95:5)	100 ˚C, 16 h	<3	96	<1

At ambient temperature in d_3-MeCN, analysis of **51** showed quantitative amounts of the fluorinating reagent (Table S3-1, entry 1). When **51** was dissolved in a 95:5 d_3-MeCN:d_6-DMSO and analysed by ^{1}H NMR, 18% decomposition of the F^+ reagent occurred within minutes (Table S3-1, entry 2). On heating to 100 ^{o}C for 16 h, a significant conversion of **51** to the reduced **51a** observed (Table S3-1, entry 3), indicating a severe reduction in F^+ activity after heating in a MeCN/DMSO mixture.

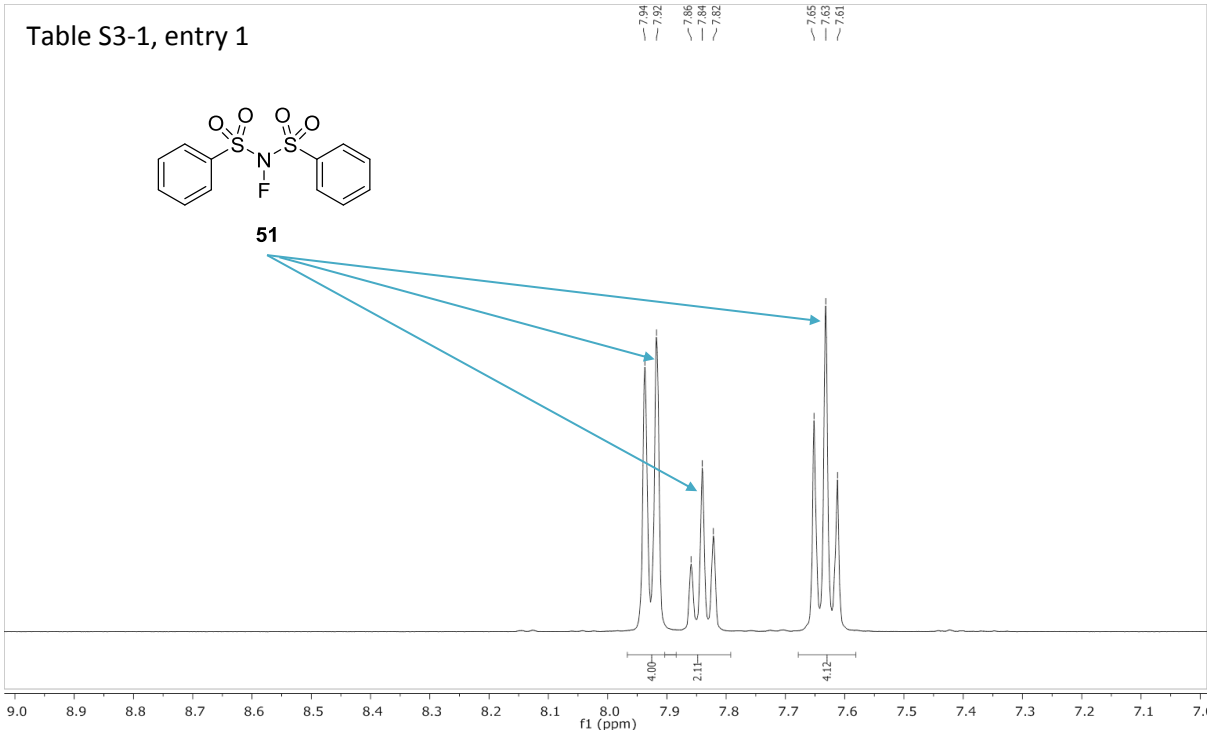


Table S3-1, entry 2

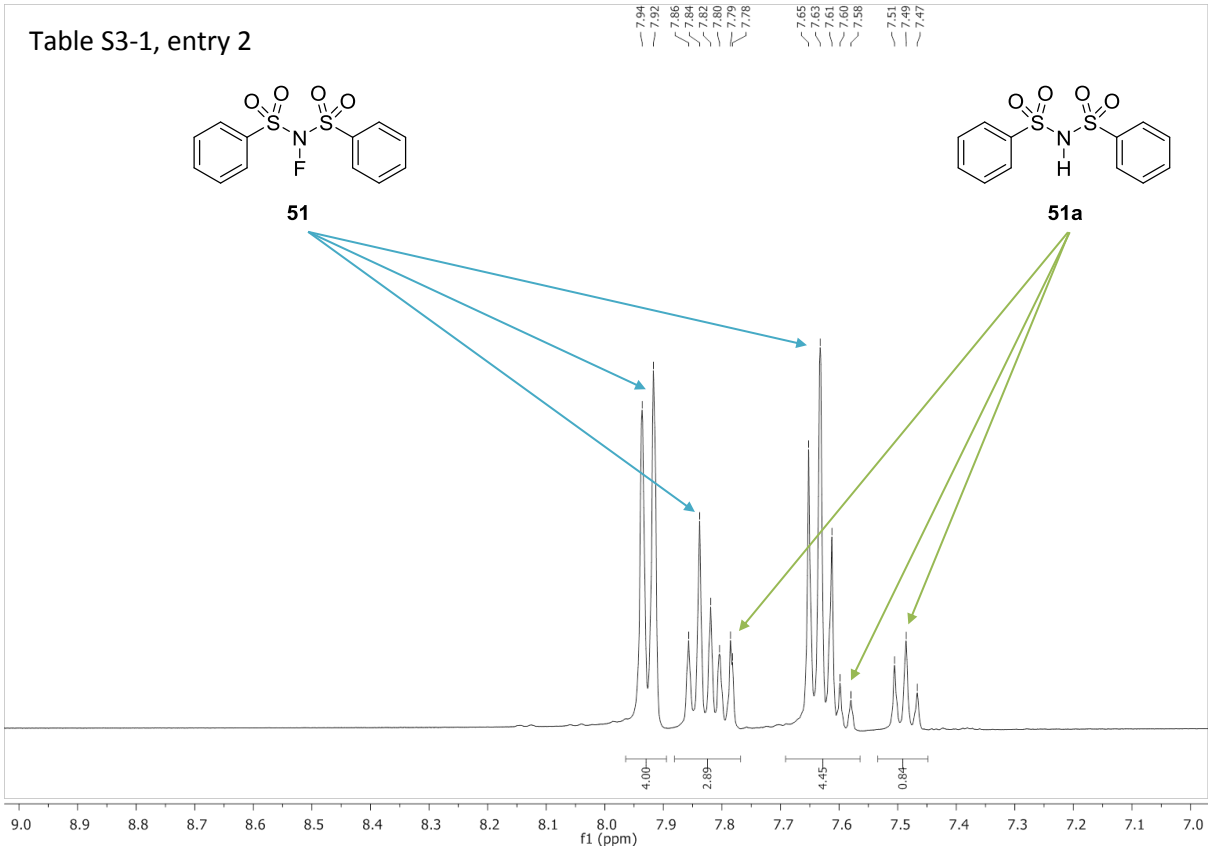


Table S3-1, entry 3

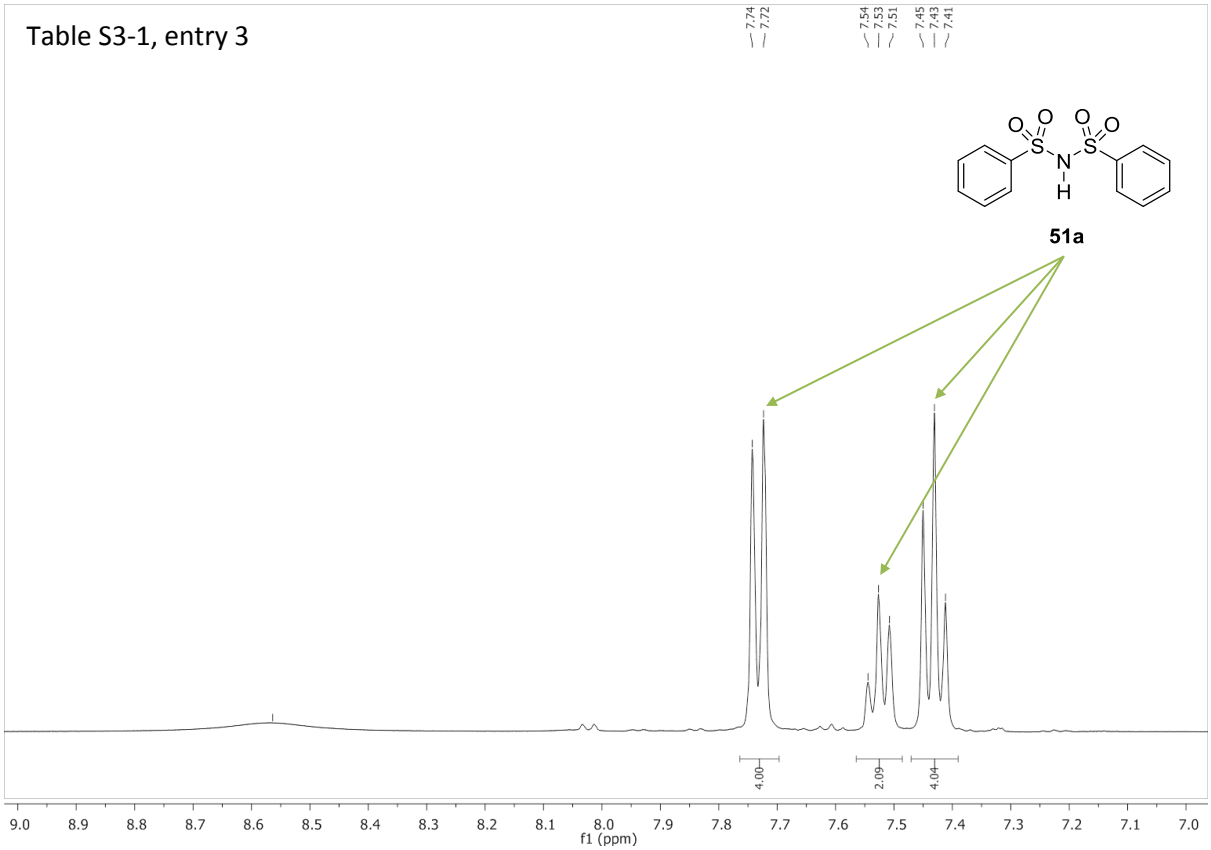
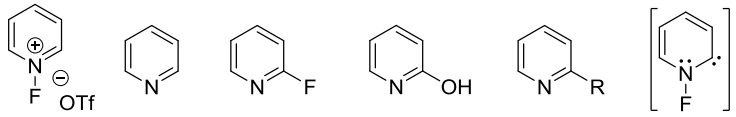


Table S3-2. Transformations of **53-OTf** in the presence of DMSO at ambient and high temperatures



53-OTf **53a** **53b** **53c** **53d** **53-I**

Entry	Solvent	Conditions	^{1}H NMR Yield (%)			
			53-OTf	**53a**	**53b**	**Other**
1	d_3-MeCN	RT	>99	0	0	0
2	d_3-MeCN: d_6-DMSO (95:5)	RT	93	0	0	4 unknown compounds of structure **53d**[a] (1-6%)
3	d_3-MeCN: d_6-DMSO (95:5)	100 ˚C, 16 h	0	48	37	**53c** 14%; unknown compound of structure **53d**[a] (2%)

[a]The formation of these compounds are consistent with the formation of a putative carbene **14** the formation of which was previously proposed by Umemoto.[226]

When **53-OTf** was dissolved in d_3-MeCN, no decomposition occurred (Table S3-2, entry 1). However, when **53-OTf** was dissolved in a 95:5 mixture of d_3-MeCN and d_6-DMSO, a small decomposition (~6%) was observed (Table S3-2, entry 2). However, on heating to 100 ˚C for 16 h all the starting material is converted non-fluorine containing pyridine **53a** or non-F^+ active 2-fluoro pyridine **53b** (Table S3-2, entry 3), with other α-substituted by-products (**53c** and **53d**-type compounds) observed in small quantities. The occurrence of these α-substituted compounds is attributed to the formation of a putative carbene intermediate **53-I** which was previously proposed by Umemoto *et al.* to account for the formation of 2-fluoropyridine **53b**, 2-pyridinol **53c** and 2-pyridyl triflate when **53-OTf** decomposes in the presence of base at room temperature.[226]

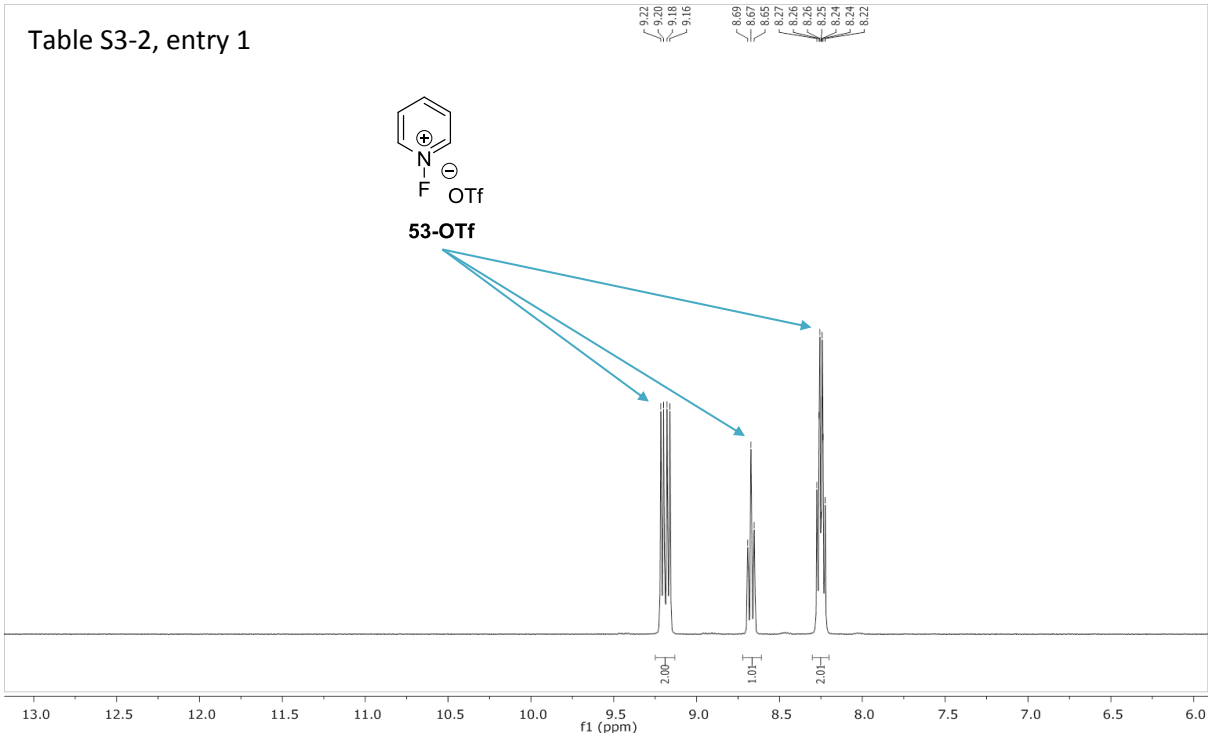


Table S3-2, entry 2

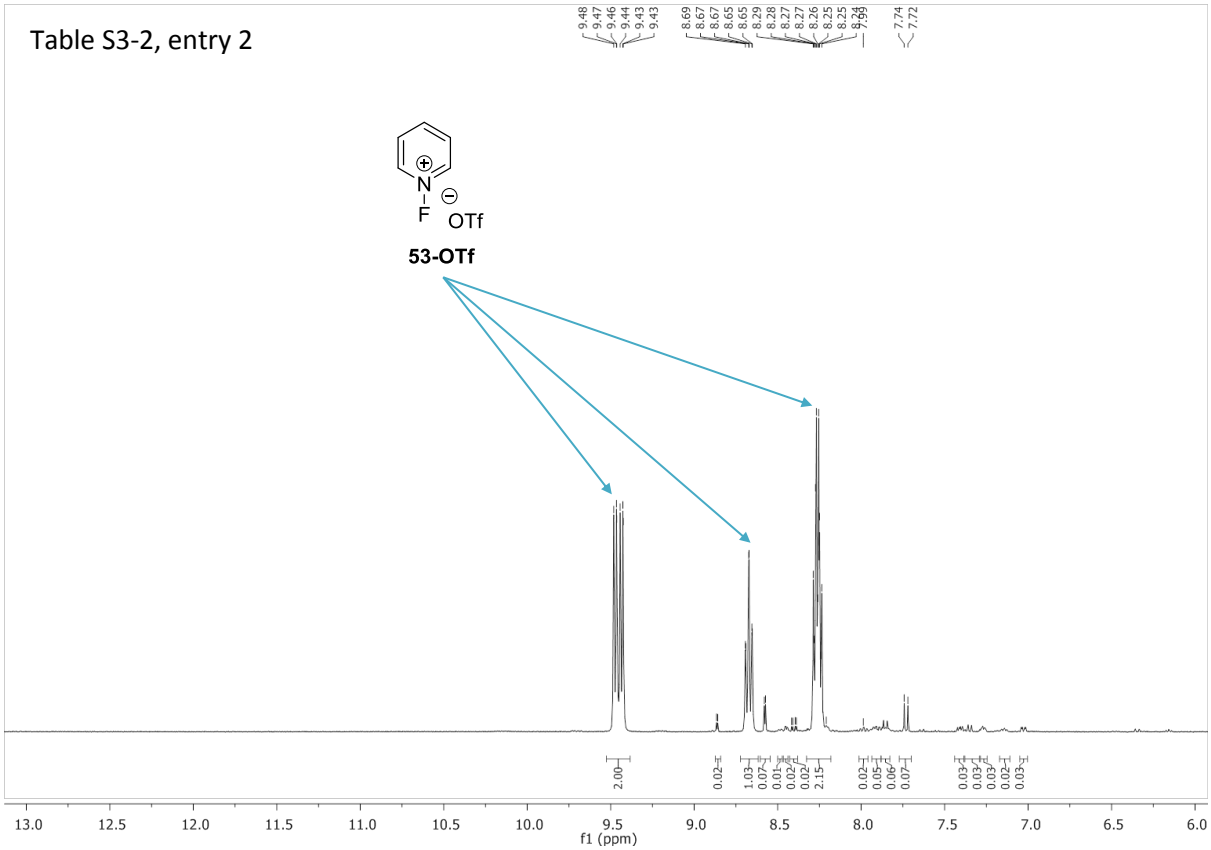


Table S3-2, entry 3

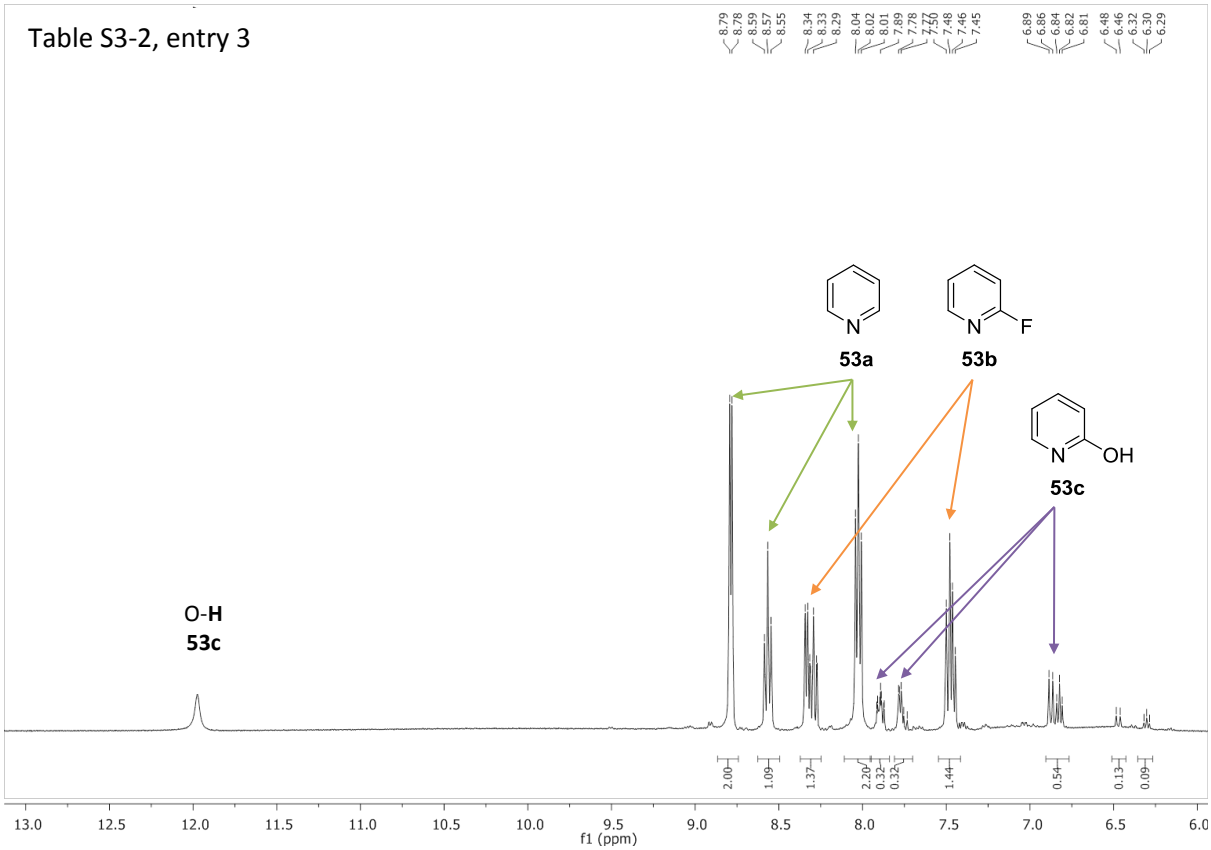
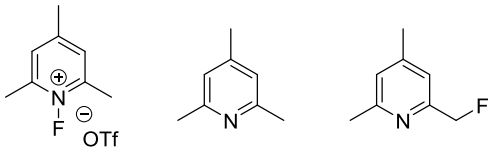


Table S3-3. Transformations of 54-**OTf** in the presence of DMSO at ambient and high temperatures



54-OTf **54a** **54b**

Entry	Solvent	Conditions	^{1}H NMR Yield (%)		
			54-OTf	**54a**	**54b**
1	d_3-MeCN	RT	98	0	2
2	d_3-MeCN:d_6-DMSO (95:5)	RT	98	0	2
3	d_3-MeCN:d_6-DMSO (95:5)	100 ˚C for 16 h	3	88	8

Similar to the case of **54-OTf**, the other *N*-fluoro pyridinium reagent **54-OTf** appears to be stable in dilute solutions of DMSO, at room temperature (Table S3-3, entry 1). At room temperature in d_3-MeCN around 2% of a fluorinated by-product (structure attributed to **54b**) is observed (Table III, entry 1). When **9-OTf** is dissolved in dilute DMSO solution, then same product distribution is observed (Table S3-3, entry 2). However, when heated to high temperatures (100 ˚C) for prolonged periods (16 h) **54-OTf** decomposes with around 3% of the original fluorinating agent being observed by ^{1}H NMR (Table S3-3, entry 3). The main decomposition product is 2,4,6-trimethyl pyridine **54a** (88%) with the structure of the minor by-product thought to be **54b**. Conclusive spectroscopic precedent for this compound could not be found, however the observation of a doublet around 5.7 ppm with a large *J* value is indicative of a CH_2F group attached to a heteroarene.[227]

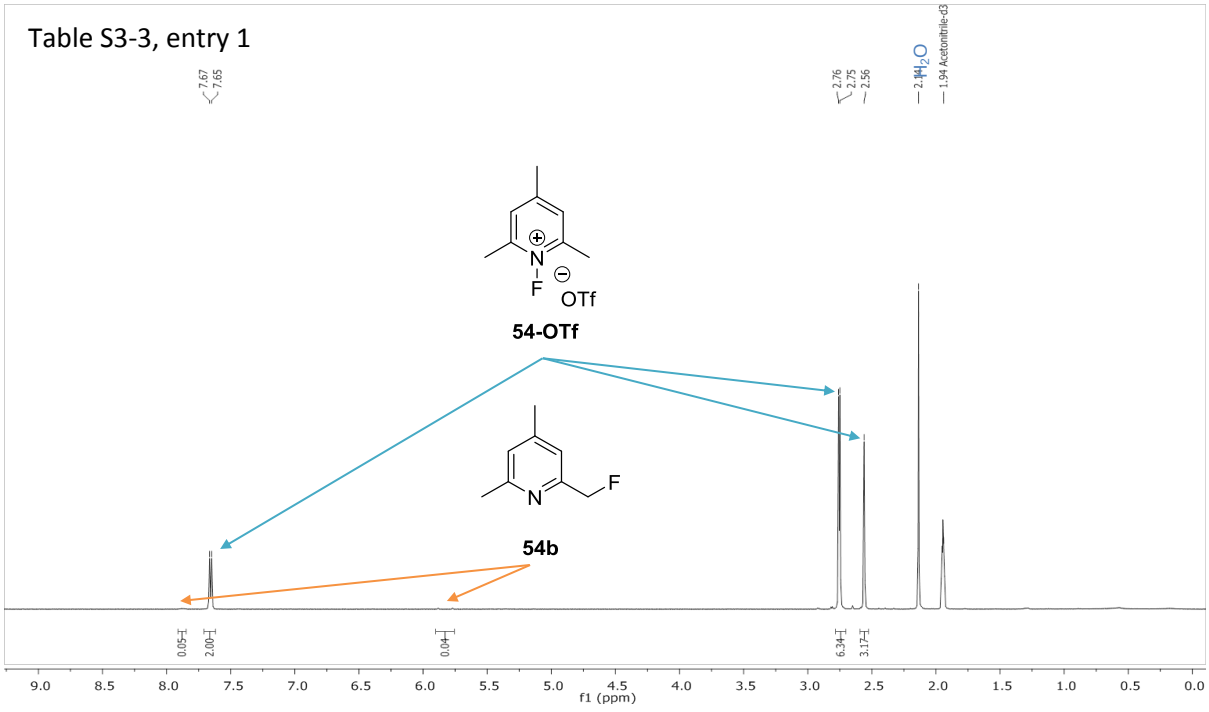


Table S3-3, entry 2

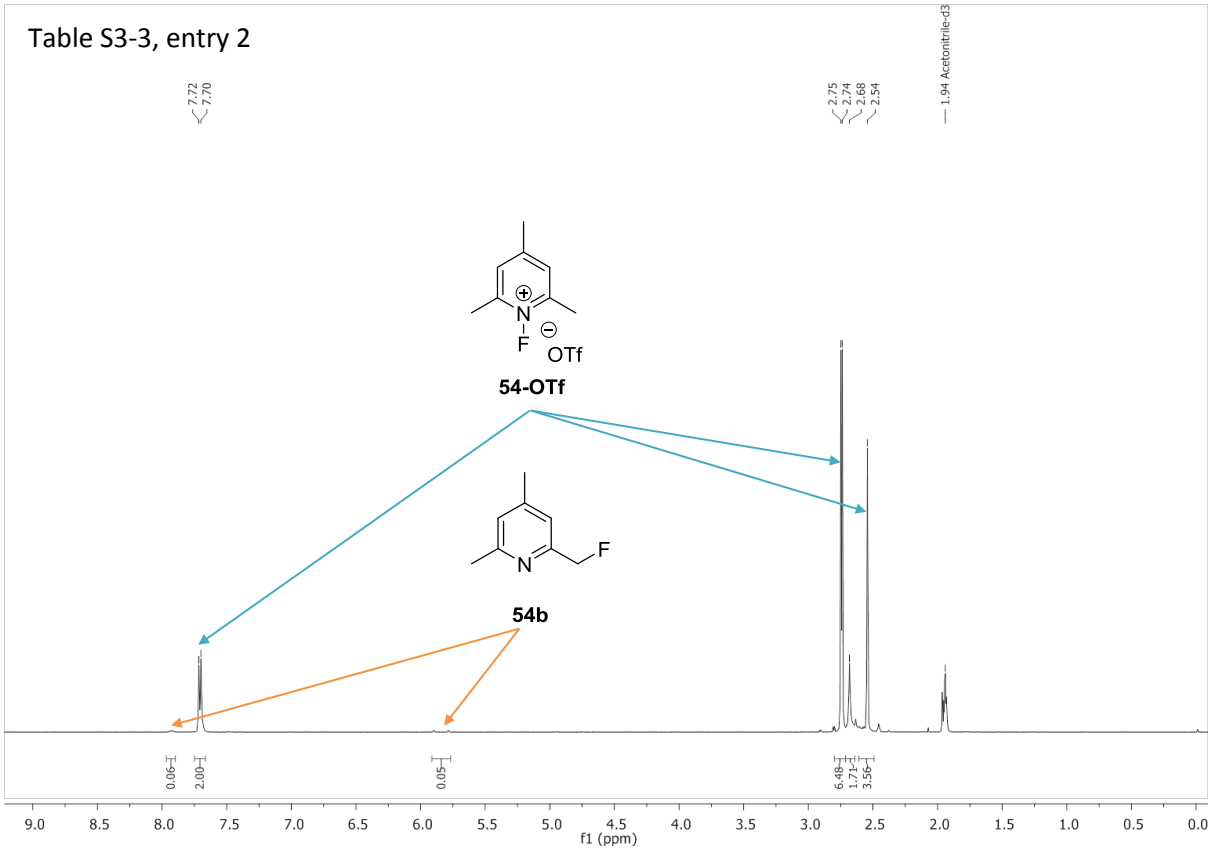


Table S3-3, entry 3

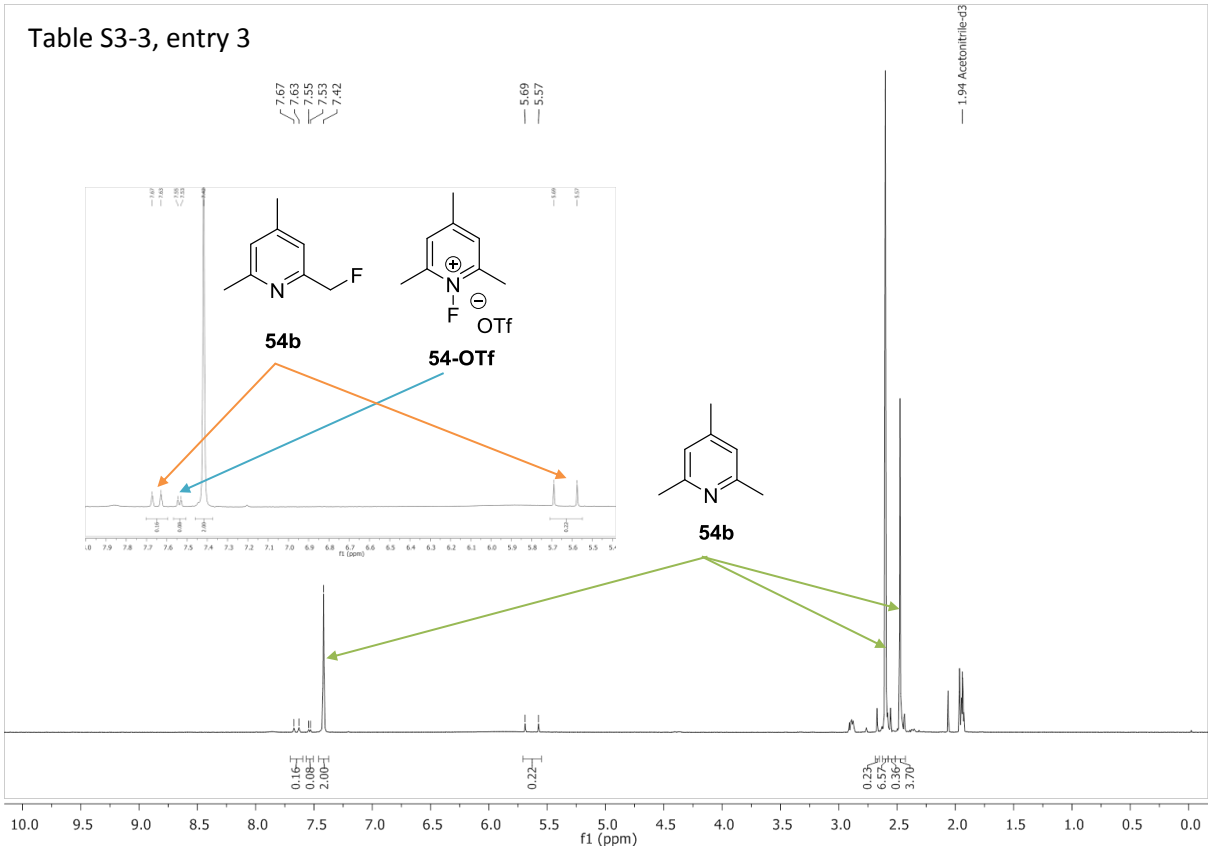
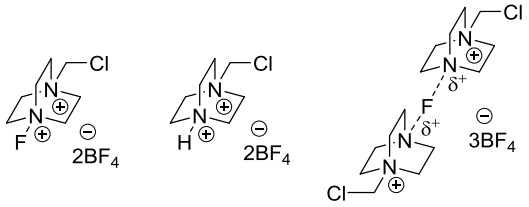


Table S3-4. Transformations of **55** in the presence of DMSO at ambient and high temperatures



55 **55a** **55b**

Entry	Solvent	Conditions	^{1}H NMR Yield (%)			
			55	**55a**	**55b**	**Other**
1	d_3-MeCN	RT	>99	0	0	-
2	d_3-MeCN:d_6-DMSO (95:5)	RT	0	68	18[a]	Σ10% three unknown by-products
3	d_3-MeCN:d_6-DMSO (95:5)	100 ˚C for 16 h	0	78	12[a]	unknown by-products, one major = 10%

[a]Proposed structure consistent with literature precedent[228]

From analysis of the spectra, it is clear that even at room temperature and low concentrations, DMSO has a detrimental effect of the F^+ activity of Selectfluor (Table S3-4, entry 2) with no free starting material being observed by ^{1}H NMR after a few minutes. Instead, the free acid **55a** with characteristic N—H proton and the putative dimer **55b** are observed in 68% and 18% yields, respectively. The existence of the dimer was previously reported by Laali *et al.* and is thought to be ineffective for F^+ transfer.[228] In experiment corresponding to entry the dimer was characterised via the observed line broadening of the proton signals which could arise through overlap of two near identical sets of signals or through the fluxional charge distribution along the N·····F·····N bond perturbing the proton environments, and the upfield shift in protons on the backbone which would be consistent with the deshielding effect experienced through dative bond formation to the fluorine atom. Two further compounds were observed but could not be fully elucidated. On heating, no other major transformations were observed except the detection of an increased amount of **55a** from 68% to 78% (Table S3-4, cf. entries 2 and 3) which could result from dissociation of the free base from the dimer, then protonation. The increase in **55a** is accompanied with a decrease in yield of the dimer (**55b**) from 18% to 12%. The proton signals from the dimer did not shift field on heating but appear to coalesce into a singlet, however the reasoning behind this observed transformation is not known.

Table S3-4, entry 1

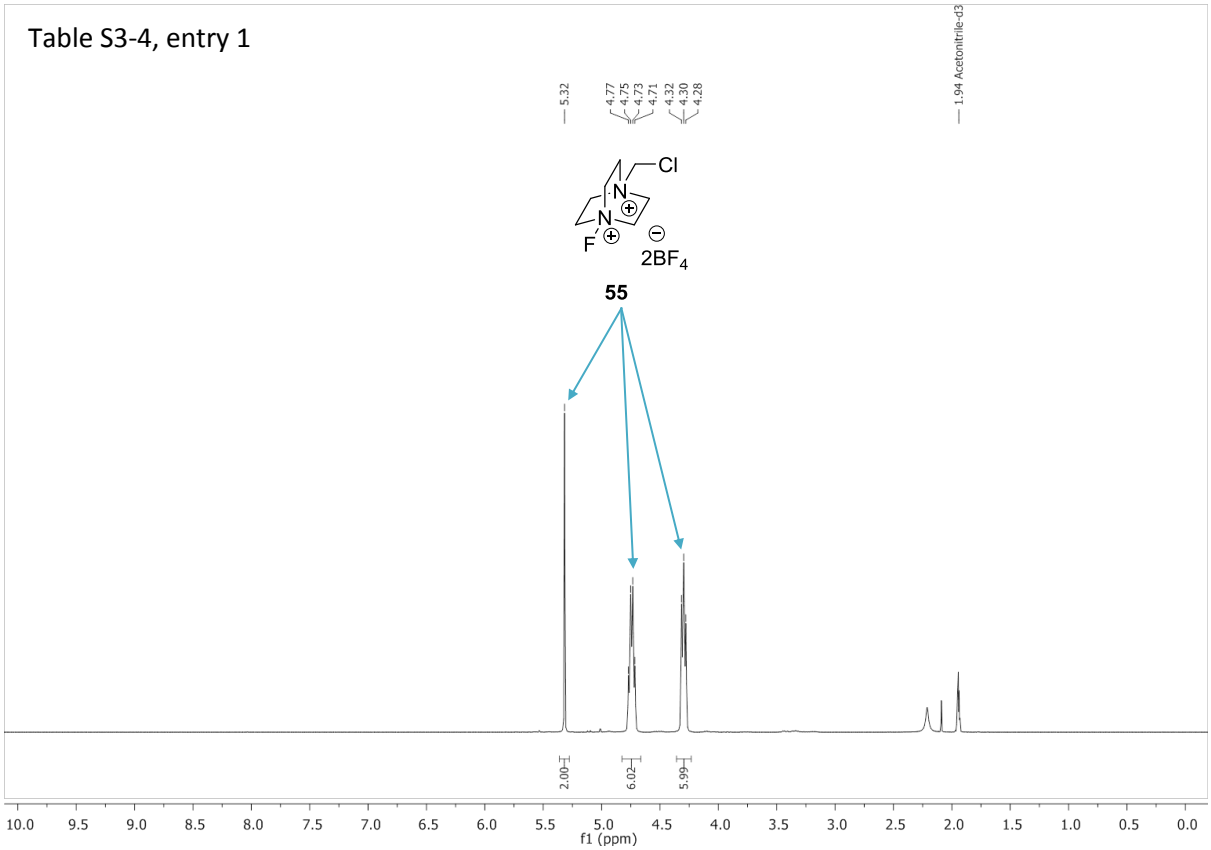
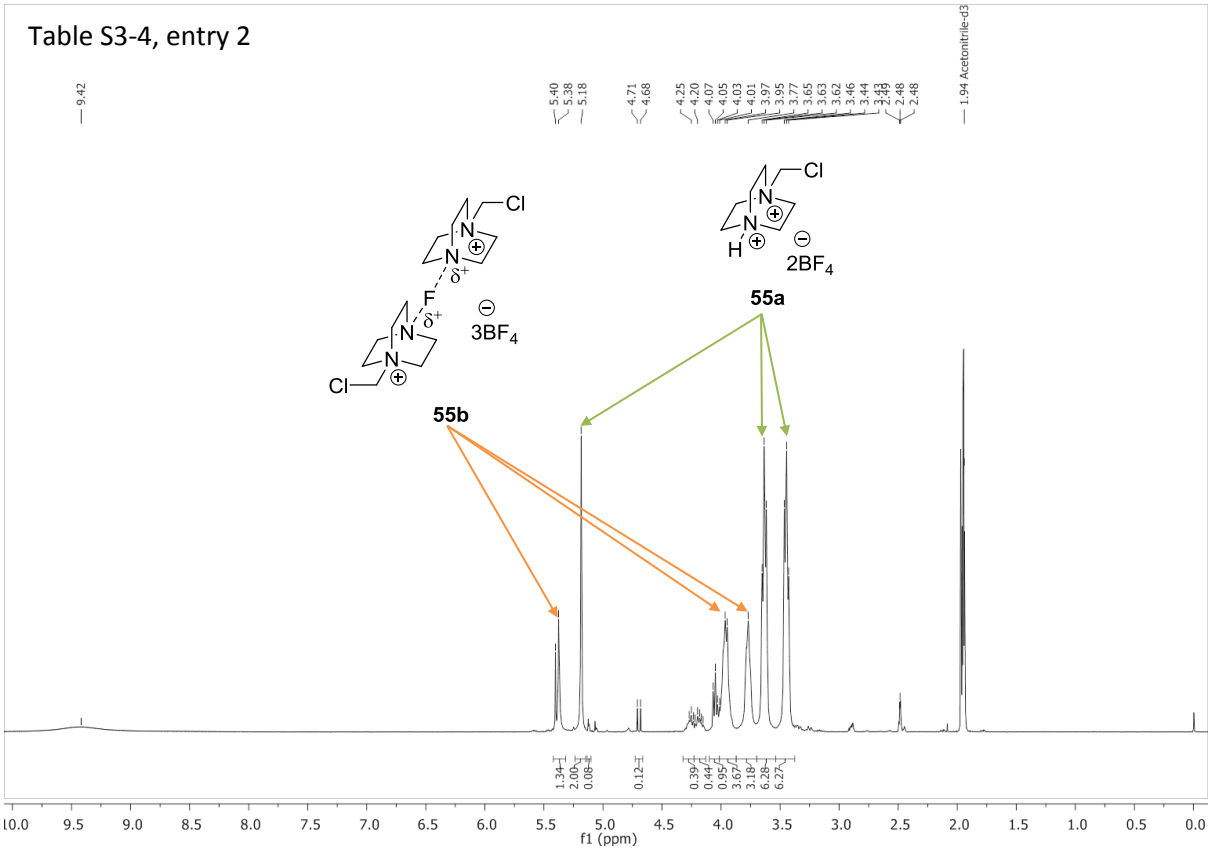
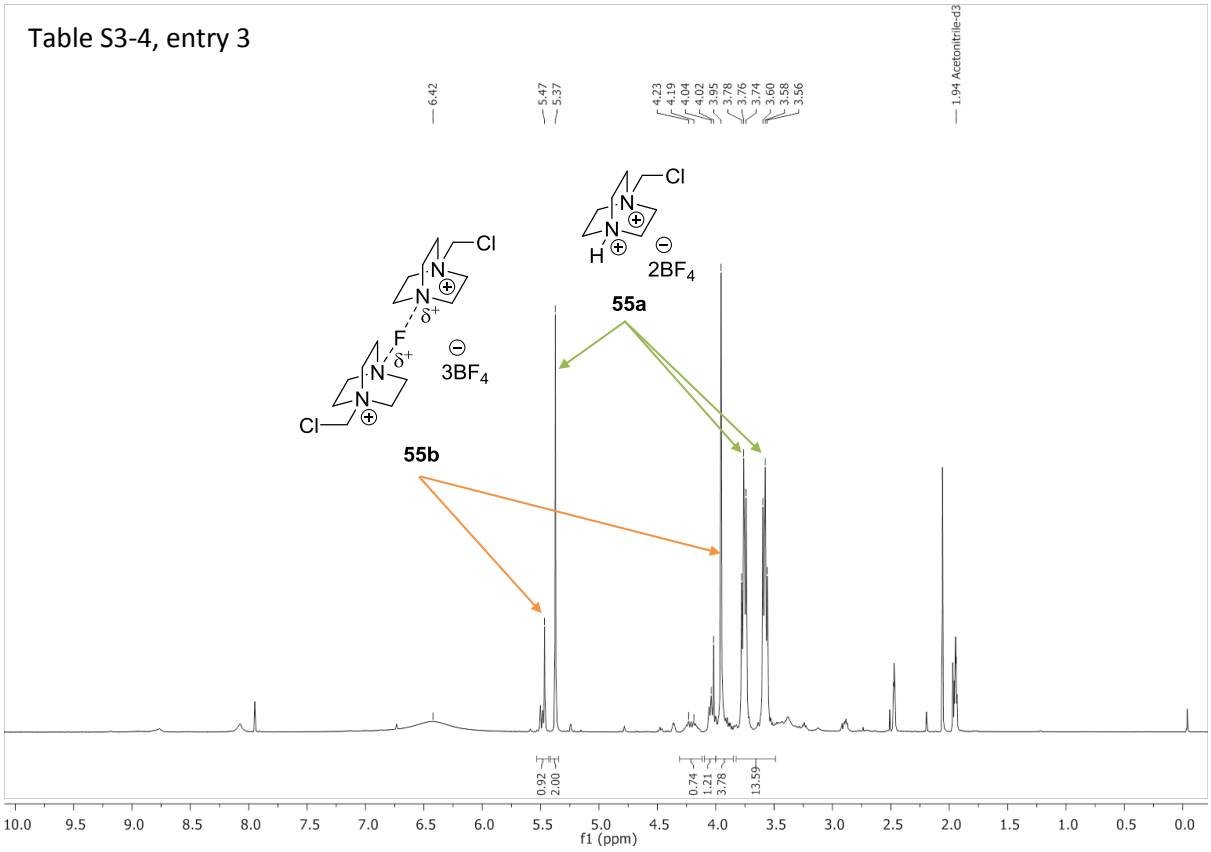


Table S3-4, entry 2





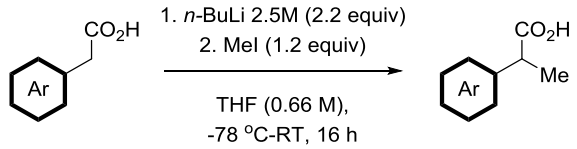
S3.2. GENERAL INFORMATION

Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. Column chromatography was carried out on silica gel, particle size 40-63 µm, using flash techniques. Deionized water was obtained from a Pure Lab Option Elga DV35 purification system. Compounds that were not commercially available were synthesised as detailed. Column chromatography was carried out using a Biotage Isolera Four purification system using Biotage ZIP® or SNAP® columns. Analytical thin layer chromatography was performed on pre-coated silica gel F_{254} plates with visualization under UV light and potassium permanganate solution. IR spectra were recorded using a Bruker Tensor 37 FTIR machine using the thin film method and are quoted in cm^{-1}. High resolution mass spectra were performed at the EPSRC National Mass Spectrometry Service Centre, Swansea. NMR spectra were recorded on a Bruker AV400 or AVIII400 sprectrometer. ^{1}H NMR spectra, recorded at 400 MHz, are referenced to the residual solvent peak at 7.26 ppm ($CHCl_3$) and quoted in ppm to 2 decimal places with coupling constants (*J*) to the nearest 0.1 Hz. ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the solvent peak at 77.16 ppm ($CDCl_3$) and quoted in ppm to 1 decimal place with coupling constants (*J*) to the nearest 0.1 Hz. ^{19}F NMR spectra were recorded at 376 MHz.

S3.3. STARTING MATERIAL PREPARATION

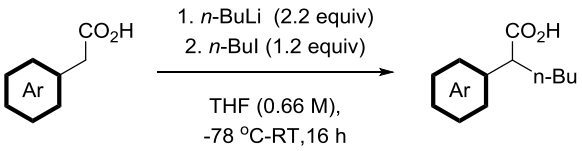
S3.3.1. General procedures

General Procedure A



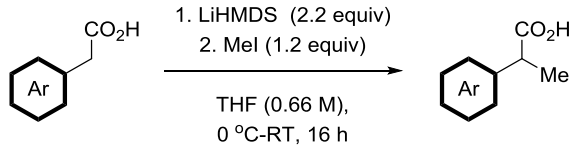
n-BuLi (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at -78 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. MeI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **98** & **99.**

General Procedure B



n-BuLi (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at -78 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. *n*-BuI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **93.**

General Procedure C

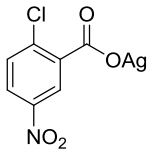


LiHMDS (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at 0 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. MeI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **97.**

S3.3.2 Starting materials

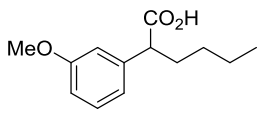
2-Phenylpropionic acid **92**, 2-(3-benzoylphenyl)propanoic acid (Ketoprofen) **95** and 2-Fluoro-alpha-methyl-4-biphenylacetic acid (Flurbiprofen) **96** are commercially available.

Silver 2-chloro-5-nitrobenzoate Ag-17



A solution of NaOH (0.080 g, 2.0 mmol) in 3 mL of H_2O was added dropwise to a solution of 2-nitro-5-chlorobenzoic acid (0.411 g, 2.0 mmol) in 4 mL of H_2O, and the mixture was stirred at room temperature for 30 min. After this time, a solution of $AgNO_3$ (0.357 g, 2.1 mmol) in 0.5 mL of H_2O was added and stirred for 1 h. Then the precipitate was filtered with exclusion of light, washed with H_2O (2 × 2 ml), then EtOH (2 mL), then Et_2O (mL) and dried *in vacuo* at 50 °C to afford **Ag-17** as an amorphous white solid (0.371 g, 60%). ^{1}H NMR (400 MHz, DMSO) δ 8.27 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.7, 2.7 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.6, 145.9, 141.4, 136.9, 131.1, 123.8, 123.4.

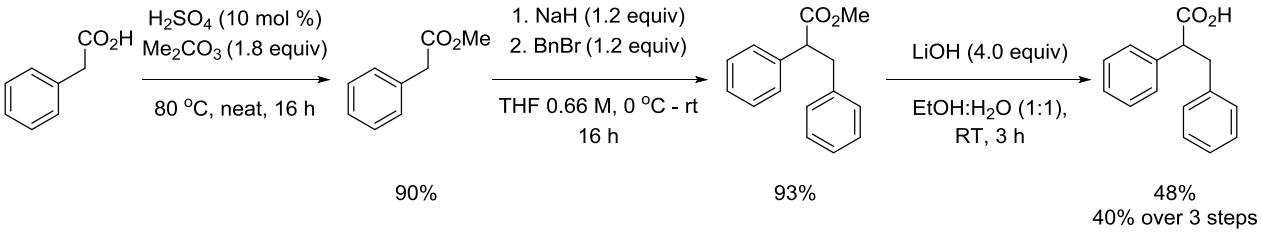
2-(3-(methoxy)phenyl)hexanoic acid 93

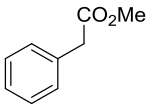


General procedure B was applied with 2-(3-(methoxy)phenyl)acetic acid (3.4 g, 20 mmol), *n*-BuLi 2.5M (17.6 mL, 44 mmol) and *n*-BuI (2.8 mL, 24 mmol) in THF (30 mL). The crude was purified by automated column chromatography eluting a gradient of 100 % hexane to 50:50 hexane:Et_2O to afford **93** as an viscous yellow oil (3.91 g,

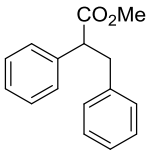
88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H, COOH), 7.24 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.88 (t, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.81 (s, 3H), 3.51 (t, *J* = 7.7 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.83 – 1.75 (m, 1H), 1.38 – 1.20 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 159.9, 140.3, 129.7, 120.6, 114.0, 112.9, 55.4, 51.7, 32.9, 29.8, 22.6, 14.0. IR: *ν*max (cm^{-1}) = 3000 (O−H), 2955 (C−H), 1702 (C=O), 1258 (C−O aryl ether), 1151 (C−O alkyl ether), 694 (C−H 1,3-disub benzene). HRMS +*p* APCI *m/z* calcd. $C_{13}H_{18}O_3$: $[M+H]^+$ = 223.1329; found = 223.1326.

2,3-diphenylpropanoic acid 94[229]

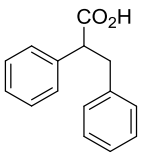




2-Phenylacetic acid (2.75 g, 20 mmol), H_2SO_4 conc (0.11 mL, 2 mmol) and Me_2CO_3 (3.06 mL, 36 mmol) were measured into a 20 mL crimp cap vial which was sealed and the reaction mixture heated to 80 °C for 16 h. After this time, the vial was cooled to room temperature and the reaction mixture partitioned with DCM (20 mL) and sat. $NaHCO_3$ solution (20 mL), the organic layer was separated and the aqueous layer extracted with DCM (2 × 15 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield an analytically pure yellowish oil (2.70 g, 90%) which was used without additional purification. Spectral data matched literature description.[230] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 5H), 3.64 (s, 3H), 3.58 (s, 2H).

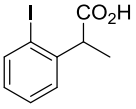


Methyl 2-phenylacetate (0.75 g, 5 mmol) in THF (5 mL) was cooled to 0 °C and added dropwise to a stirred solution of NaH (0.24 g, 6 mmol) in THF (2.5 mL) cooled in an ice bath. Following the addition the reaction mixture was stirred vigorously at this temperature for 1 h. After this time BnBr (0.72 mL, 6 mmol) was added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. The reaction was quenched with H_2O (2 mL) and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O (10 mL) partitioned with H_2O and the organic layer was separated and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield an amorphous off-white solid (1.12 g, 93%) which was used without additional purification. Spectral data matched literature description. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.01 (m, 10H), 3.81 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.54 (s, 3H), 3.37 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.98 (dd, *J* = 13.7, 6.7 Hz, 1H).[231]



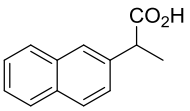
Methyl 2,3-diphenylpropanoate (1.12 g, 4.65 mmol) was dissolved in a 1:1 mixture of EtOH and H_2O (10 mL), LiOH (0.45 g, 18.6 mmol) was added and the reaction mixture stirred in an open flask for 3 hours. After this time the reaction mixture was diluted with Et_2O (10 mL) and the organic layer was separated, the aqueous was acidified with 1 M HCl and extracted with Et_2O (3 × 10 mL) . The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallisation of the crude with hexane/$CHCl_3$ afforded **94** as a amorphous white solid (0.50 g, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (br s, 1H, COOH), 7.29-7.07 (m, 10H), 3.83 (dd, *J* = 8.0, 7.3 Hz, 1H), 3.38 (dd, *J* = 13.8, 8.4 Hz, 1H), 3.01 (dd, *J* = 13.8, 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 138.8, 138.1, 129.1 (2C), 128.9 (2C), 128.5 (2C), 128.3 (2C), 127.8, 126.6, 53.6, 39.4.

2-(2-iodophenyl)propanoic acid 97[232]



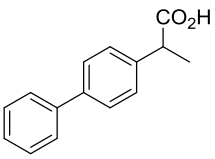
General procedure C was applied with 2-(2-iodophenyl)acetic acid (1.3 g, 5 mmol), LiHMDS (11 mL, 11 mmol, 1.0 M) and MeI (0.37 mL, 6 mmol) in THF (7.5 mL). Recrystallisation of the crude from hexane/$CHCl_3$ afforded **97** as a dark yellow amorphous solid (1.11 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 1H), 7.36 – 7.31 (m, 2H), 6.96 (ddd, *J* = 8.0, 5.6, 3.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 142.8, 139.8, 129.0, 128.8, 127.6, 101.1, 49.4, 18.0.

2-(2-Naphthyl)propanoic acid 98[233]



General procedure A was applied with 2-(2-naphthyl)acetic acid (1.9 g, 10 mmol), *n*-BuLi (8.8 mL, 22 mmol, 2.5 M) and MeI (1.17 mL, 12 mmol) in THF (15 mL). Recrystallisation of the crude with hexane/$CHCl_3$ afforded **98** as an off-white amorphous solid (1.57 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.4 (br s, 1H, COOH), 7.83-7.77 (m, 4H), 7.50-7.44 (m, 3H), 3.92 (q, *J* = 7.1 Hz, 1H), 1.62 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.7, 137.3, 133.6, 132.9, 128.6, 128.0, 127.8, 126.5, 126.4, 126.1, 125.8, 45.6, 18.3.

2-([1,1'-biphenyl]-4-yl)propanoic acid 99[234]



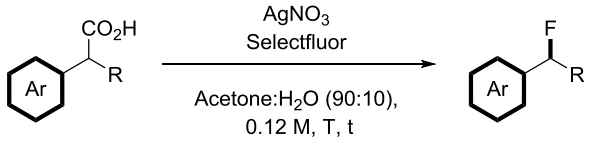
General procedure A was applied with 4-biphenylacetic acid (2.2 g, 10 mmol), *n*-BuLi (8.8 mL, 22 mmol, 2.5 M) and MeI (1.17 mL, 12 mmol) in THF (15 mL). Recrystallisation of the crude with *i*-Pr_2O afforded **99** as an off-white solid (1.50 g, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (br s, 1H, COOH), 7.60 – 7.54 (m, 4H), 7.45-7.39 (m, 4H), 7.34 (t, *J* = 7.3 Hz, 1H), 3.80 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 140.9, 140.6, 138.9, 128.9 (2C), 128.2 (2C), 127.6 (2C), 127.5, 127.2 (2C), 45.1, 18.3.

S3.4. BENZYLIC FLUORIDE PREPARATION

All reactions were carried out in accordance with general procedure D at 0.12 M concentration, unless otherwise stated. The reaction scale, amounts of $AgNO_3$ and Selectfluor, the temperature and time for each reaction are specified below. Compounds

S3.4.1. General procedure

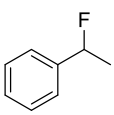
General Procedure D



Note: *when pure, benzylic fluorides can rapidly decompose in the presence of catalytic amounts of strong acids or on borosilicate glass to produce HF and polymerisation products*[235]*. Due to their instability, they should not be stored neat on borosilicate glass. They are stable in solution (eg. acetone, MeCN, $CHCl_3$ (filtered through alumina), alkanes etc.) or stored over bases. Furthermore, final evaporations after column chromatography should be carried out in a PFA rbf, or the majority of the solvent removed in a borosilicate rbf then transferred to a soda-lime glass vial or plastic centrifuge tube for the final solvent removal.*

Selectfluor (1.15 equiv) and a phenylpropanoic acid (1 equiv) were weighed into a crimp cap vial and dissolved in a 90:10 solution of acetone:H_2O. $AgNO_3$ (0.20 equiv) was added and the reaction vessel quickly sealed, covered in foil and stirred in an oil bath for the stated amount of time. After this time the reaction vessel was rapidly cooled in an ice bath and quenched with 1 M HCl to precipitate out AgCl. The reaction mixture diluted in DCM and basified with saturated K_2CO_3 solution. The organic layer was separated and the aqueous layer extracted DCM (× 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The yield was determined by ^{1}H NMR using mesitylene of 1,3,5-trimethoxybenzene as an internal standard. Products **92a-99a** were purified by automated column chromatography in the specified eluents.

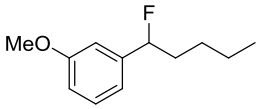
(1-fluoroethyl)benzene 92a[197b]



General procedure D was applied with **92** (0.704 mL, 5.0 mmol), Selectfluor (2.14g, 5.75 mmol), $AgNO_3$ (0.170 g, 1.0 mmol) in Acetone:H_2O (37.5 mL : 4.2 mL), heated to 90 ^oC for 5 minutes in a 100mL Ace pressure tube. The crude was purified by FCC eluting 100% pentane and volatiles removed on a rotary evaporator (~200 mBar, T_{bath}= <30 ^oC) to afford **92a** as a

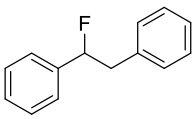
colourless oil (0.520 g, 84%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.30 (m, 5H), 5.64 (dq, *J* = 47.7, 6.4 Hz, 1H), 1.66 (dd, *J* = 23.9, 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (d, *J* = 19.5 Hz), 128.6 (2C), 128.3 (d, *J* = 2.0 Hz, 2C), 125.4 (d, *J* = 6.7 Hz), 91.1 (d, *J* = 166.9 Hz), 23.1 (d, *J* = 25.3 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) −167.1.

1-(1-fluoropentyl)-3-(methoxy)benzene 93a



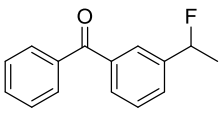
93 (4.25 g, 19.1 mmol), Selectfluor (8.2 g, 22.0 mmol), $AgNO_3$ (0.650g, 3.82 mmol) in Acetone:H_2O (0.19 M, 90 mL: 10 mL), heated to 70 °C for 1 h in a 250 mL RBF with a reflux condenser attached. The crude was purified by FCC eluting a gradient of 98:2 hexane:Et_2O to 92:8 hexane:Et_2O to afford **93a** as a colourless oil, (2.52 g, 67%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.1 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.90 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.44 (ddd, *J* = 48.0, 8.0, 4.9 Hz, 1H), 3.84 (s, 3H), 2.03 (dtd, *J* = 11.4, 8.8, 4.1 Hz, 1H), 1.87 (dddd, *J* = 19.2, 14.8, 8.5, 3.4 Hz, 1H), 1.57 – 1.46 (m, 1H), 1.46 – 1.33 (m, 3H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 142.3 (d, *J* = 19.9 Hz), 129.4, 117.7 (d, *J* = 6.9 Hz), 113.5 (d, *J* = 1.7 Hz), 111.0 (d, *J* = 7.4 Hz), 94.4 (d, *J* = 170 Hz), 55.1, 36.9 (d, *J* = 23.5 Hz), 27.2 (d, *J* = 4.3 Hz), 22.4, 13.8. ^{19}F{^{1}H] NMR (376 MHz, $CDCl_3$) δ −174.7. IR: *ν*max (cm^{-1}) = 2956 (C−H), 1588 (C=C aryl), 1262 (C−O aryl ether), 1159 (C−O alkyl ether), 1043 (C−F), 696 (C−H, 1,3-disub benzene benzene). MS (EI) *m/z* 196 (M^+ 100).

(1-fluoroethane-1,2-diyl)dibenzene 94a[236]



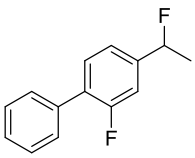
General procedure D was applied with 94 (158 mg, 0.70 mmol), Selectfluor (300 mg, 0.805 mmol), $AgNO_3$ (23.8 mg, 0.140 mmol) in Acetone:H_2O (5.25 mL : 581 µL), heated to 70 °C for 1 hour in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 95:5 hexane:Et_2O to afford **94a** as a white amorphous solid (80 mg, 57%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.11 (m, 8H), 7.13 – 7.05 (m, 2H), 5.54 (ddd, *J* = 47.4, 8.1, 4.9 Hz, 1H), 2.97-3.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (d, *J* = 19.8 Hz), 136.7 (d, *J* = 4.1 Hz), 129.5 (2C), 128.4 (3C), 128.3, 126.7, 125.7 (d, *J* = 6.6 Hz), 94.8 (d, *J* = 176 Hz), 44.1, 43.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −173.1.

(3-(1-fluoroethyl)phenyl)(phenyl)methanone 95a



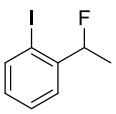
General procedure D was applied with **95** (254 mg, 1.00 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in Acetone:H_2O (7.5 mL : 830 µL), heated to 70 ^oC for 1 hour in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:Et_2O to 90:10 hexane:Et_2O to afford **95a** as a colourless oil, (163 mg, 75 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 3H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.52 – 7.45 (m, 3H), 5.69 (dq, *J* = 47.5, 6.4 Hz, 1H), 1.66 (dd, *J* = 23.9, 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 142.0 (d, *J* = 19.9 Hz), 138.0, 137.5, 132.6, 130.1 (2C), 130.0 (d, *J* = 1.7 Hz), 129.2 (d, *J* = 6.8 Hz), 128.6, 128.4 (2C), 126.7 (d, *J* = 6.9 Hz), 90.5 (d, *J* = 169 Hz), 23.0 (d, *J* = 25.0 Hz). $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ −168.5. IR: *v*max (cm^{-1}) = 2983 (C−H), 1658 (C=O), 1597 (C−C), 1066 (C−F), 719 (1,3-disub benzene), 699 (monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{15}H_{13}FO$: $[M+H]^+$ = 229.1023; found = 229.1022.

2-fluoro-4-(1-fluoroethyl)-1,1'-biphenyl 96a



General procedure D was applied with **96** (247 mg, 1.00 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in Acetone:H_2O (7.5 mL : 830 µL), heated to 50 ^oC for 1 hour in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:DCM to 80:20 hexane:DCM to afford **96a** as a colourless oil, (163 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 3H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.23 – 7.13 (m, 2H), 5.67 (dq, *J* = 47.5, 6.4 Hz, 1H), 1.69 (dd, *J* = 23.9, 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (d, *J* = 248 Hz), 143.1 (dd, *J* = 20.3, 7.5 Hz), 135.5, 131.0 (d, *J* = 3.8 Hz), 129.1 (2C), 128.9 (app q, *J* = 11.0, 13.9 Hz), 128.6 (2C), 127.9, 121.2 (dd, *J* = 6.8, 3.4 Hz), 113.14 (dd, *J* = 24.2, 7.4 Hz), 90.1 (d, *J* = 169.6 Hz, 1C), 22.9 (d, *J* = 25.3 Hz, 1C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) −117.3, −168.3. IR: *v*max (cm^{-1}) = 2984 (C−H), 1485 (C=C aryl), 1416 (C=C aryl), 1068 (C−F), 1011 (C−F), 865 (C−H, 1,2,4-trisub benzene), 696 (monosub benzene). HRMS +*p* APCI *m/z* calcd $C_{14}H_{12}F_2$: $[M]^+$ = 218.0902; found = 218.0897.

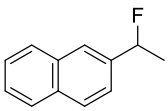
1-(1-fluoroethyl)-2-iodobenzene 97a



53 (82.8 mg, 0.30 mmol), Selectfluor (129 mg, 1.15 mmol), $AgNO_3$ (15.3 mg, 0.09 mmol) in Acetone:H_2O (7.5 mL : 830 µL) were heated to 90 ^oC for 2 hour in a 10 mL crimp cap vial. **97a** could not be obtained pure after FCC in 100% hexane, the yield was calculated by ^1H NMR, using 1,3,5-trimethoxybenzene as an internal standard (74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.01 (td, *J* = 7.7, 1.6 Hz, 1H), 5.74 (dt, *J* = 46.4, 6.3 Hz, 1H), 1.61 (dd, *J* = 24.0, 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2

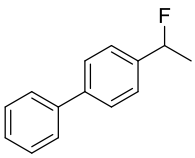
(d, *J* = 19.4 Hz), 139.5, 129.9 (d, *J* = 1.3 Hz), 128.9, 126.3, 126.2, 95.4 (d, *J* = 169 Hz), 22.4 (d, *J* = 25.8 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ −171.0.

2-(1-fluoroethyl)naphthalene 98a[227]



General procedure D was applied with 98 (140 mg, 0.70 mmol), Selectfluor (300 mg, 0.805 mmol), $AgNO_3$ (23.8 mg, 0.14 mmol) in Acetone:H_2O (5.25mL :581 µL), heated to 70 °C for 30 mins in a 10 mL crimp cap vial. The crude was purified by FCC eluting 100% hexane to afford **98** as an amorphous white solid (63 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.75 (m, 4H), 7.58 – 7.44 (m, 3H), 5.81 (dq, *J* = 47.6, 6.4 Hz, 1H), 1.74 (dd, *J* = 23.8, 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (d, *J* = 19.4 Hz), 133.2 (d, *J* = 1.4 Hz) , 133.1, 128.4, 128.1, 127.7, 126.3, 126.2, 124.2 (d, *J* = 8.0 Hz), 123.1 (d, *J* = 5.8 Hz), 91.1 (d, *J* =167 Hz), 22.9 (d, *J* =25.0 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ −167.0.

4-(1-fluoroethyl)-1,1'-biphenyl 99a[211]

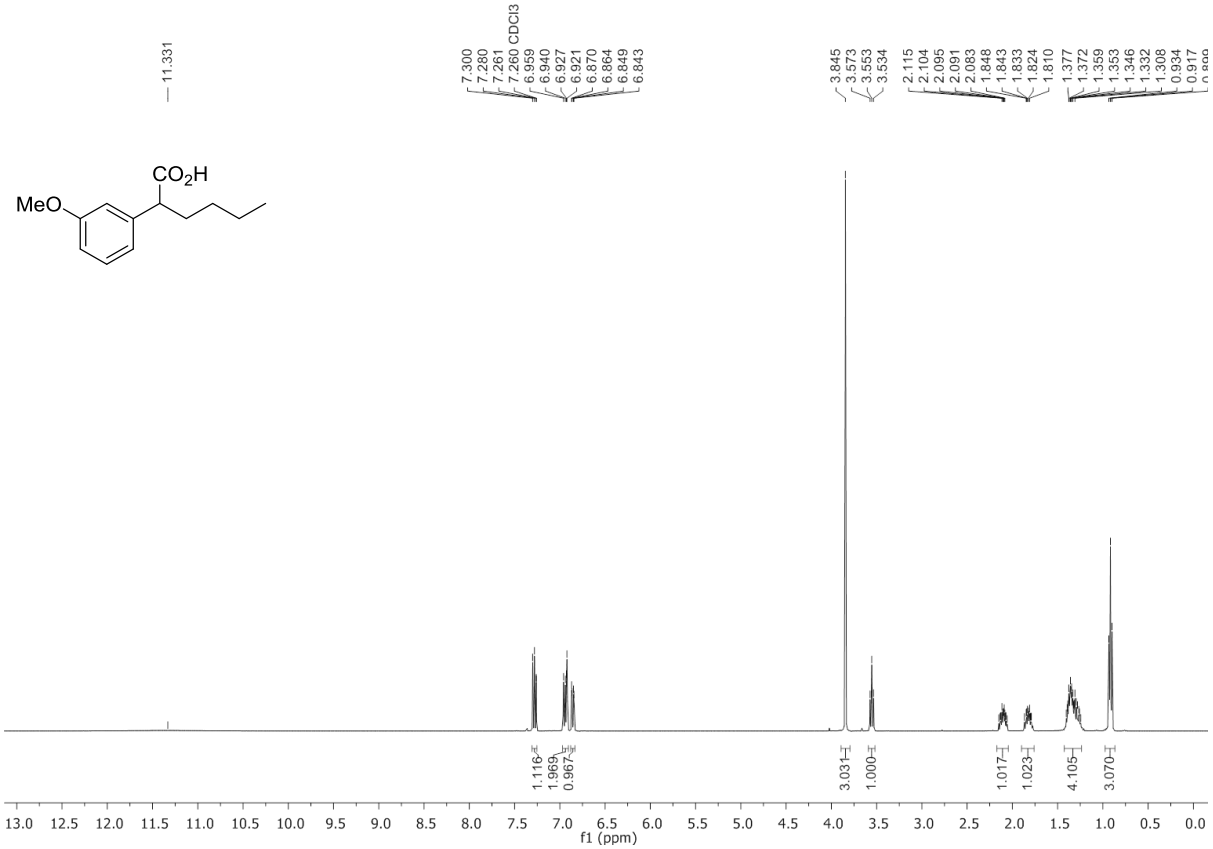


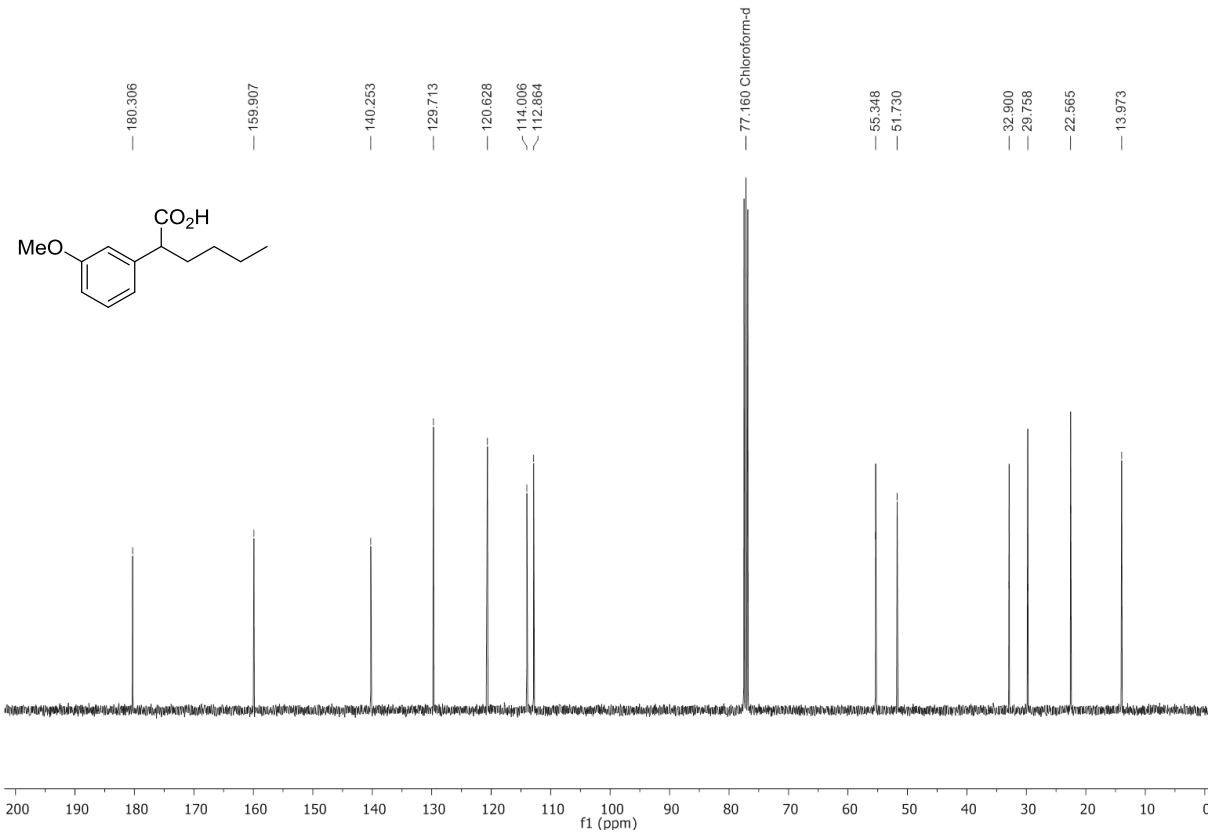
General procedure D was applied with **99** (22.6 mg, 0.10 mmol), Selectfluor (42.9 mg, 0.115 mmol), $AgNO_3$ (3.4 mg, 0.02 mmol) in Acetone:H_2O (750 µL: 83 µL), heated to 70 °C for 30 mins in a 10 mL crimp cap vial. The yield of **99a** was calculated by ^{1}H NMR, using 1,3,5-trimethoxybenzene as an internal standard (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 − 7.46 (m, 5H), 7.39 − 7.20 (m, 4H), 5.58 (dq, *J* = 47.7, 6.4 Hz, 1H), 1.56 (dd, *J* = 23.7, 6.5 Hz, 3H). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) −166.8.

The yields of compounds **97a** and **99a** were calculated via ^{1}H NMR using an internal standard and product identity confirmed by GC-MS or against known spectra.[211] Compound **97a** co-eluted with apolar by-products in 100% hexane and could not be obtained pure. Compound **99a** decomposed on isolation.

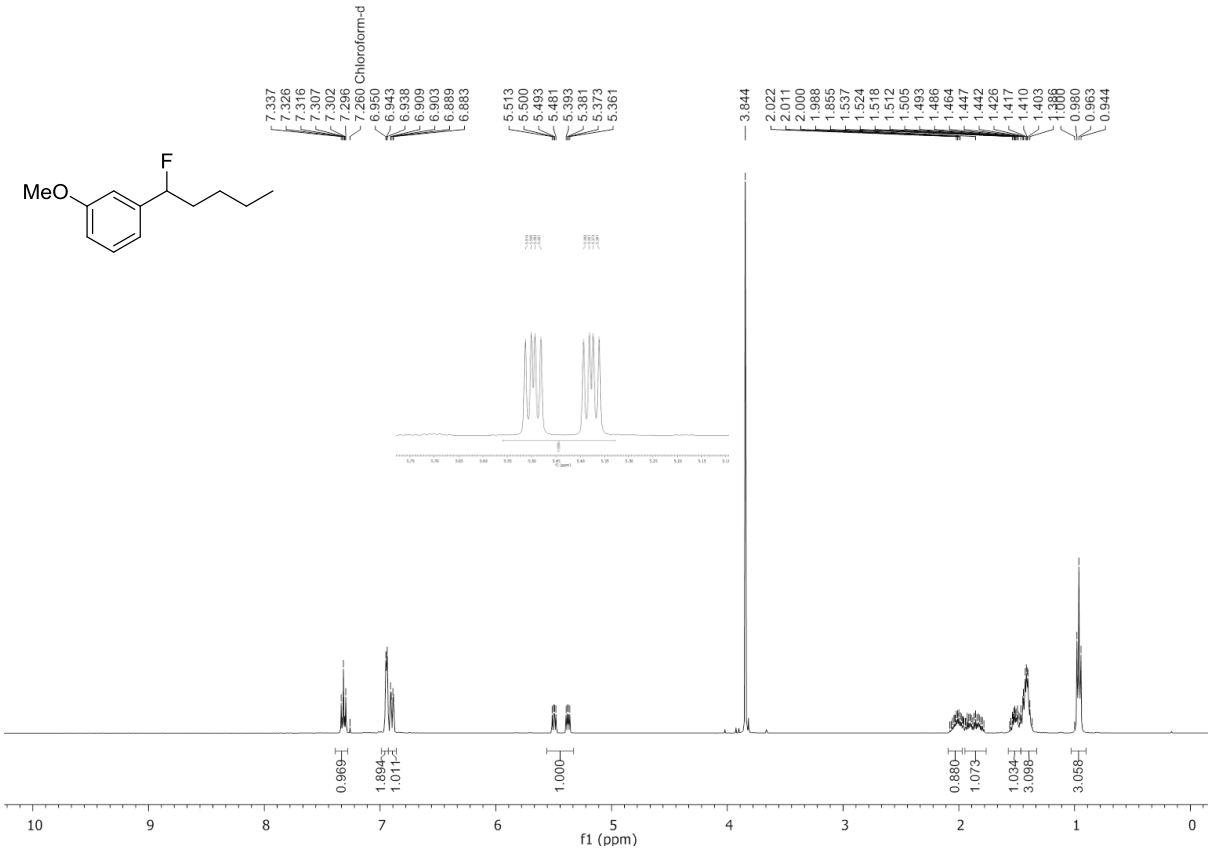
S3.5. SPECTRA OF NEW COMPOUNDS

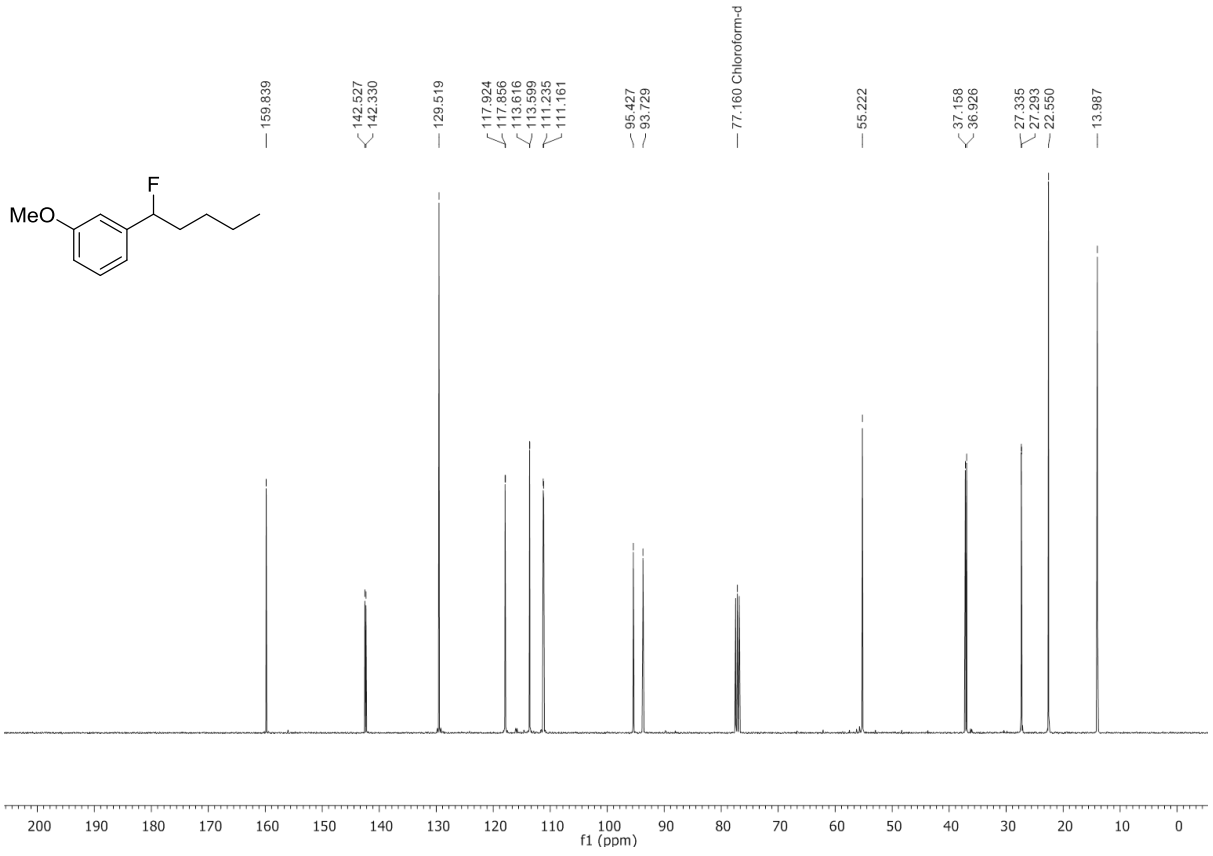
2-(3-(methoxy)phenyl)hexanoic acid **93**

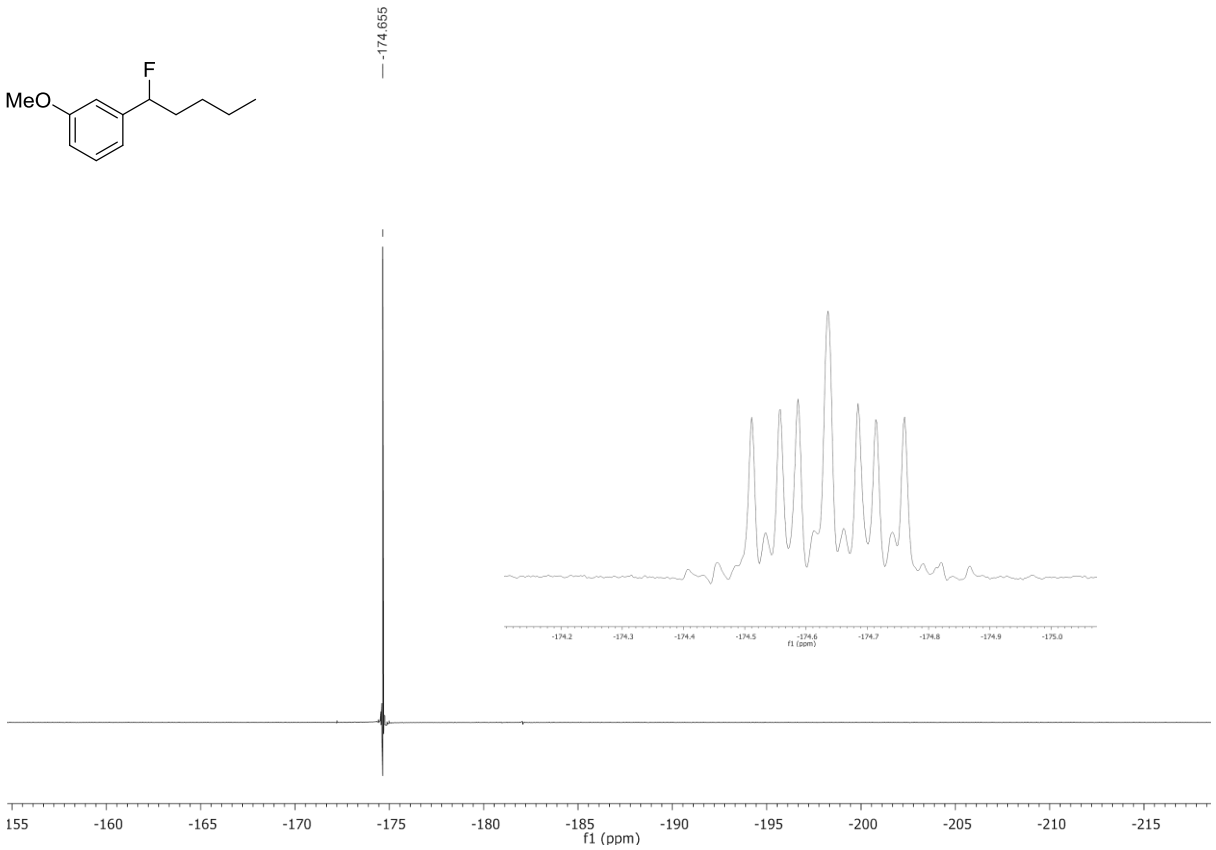




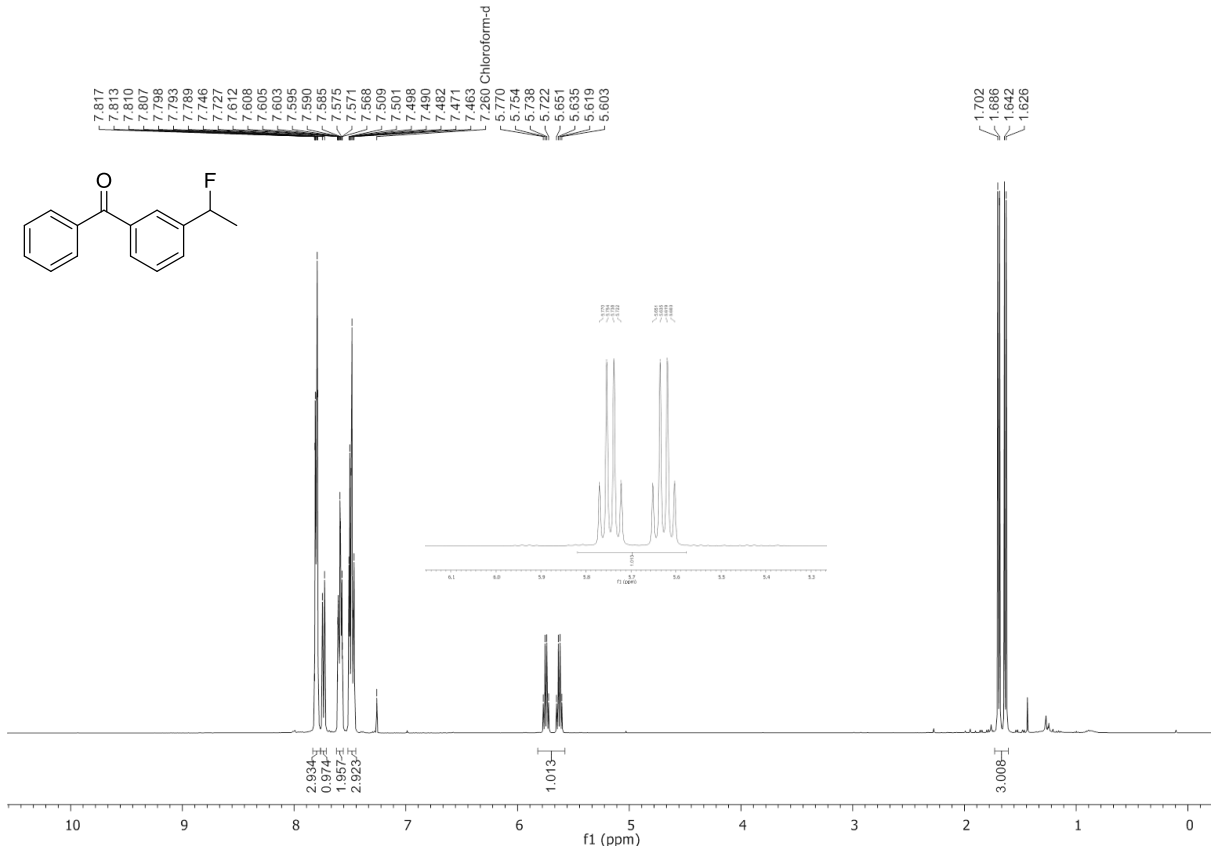
1-(1-fluoropentyl)-3-(methoxy)benzene **93a**

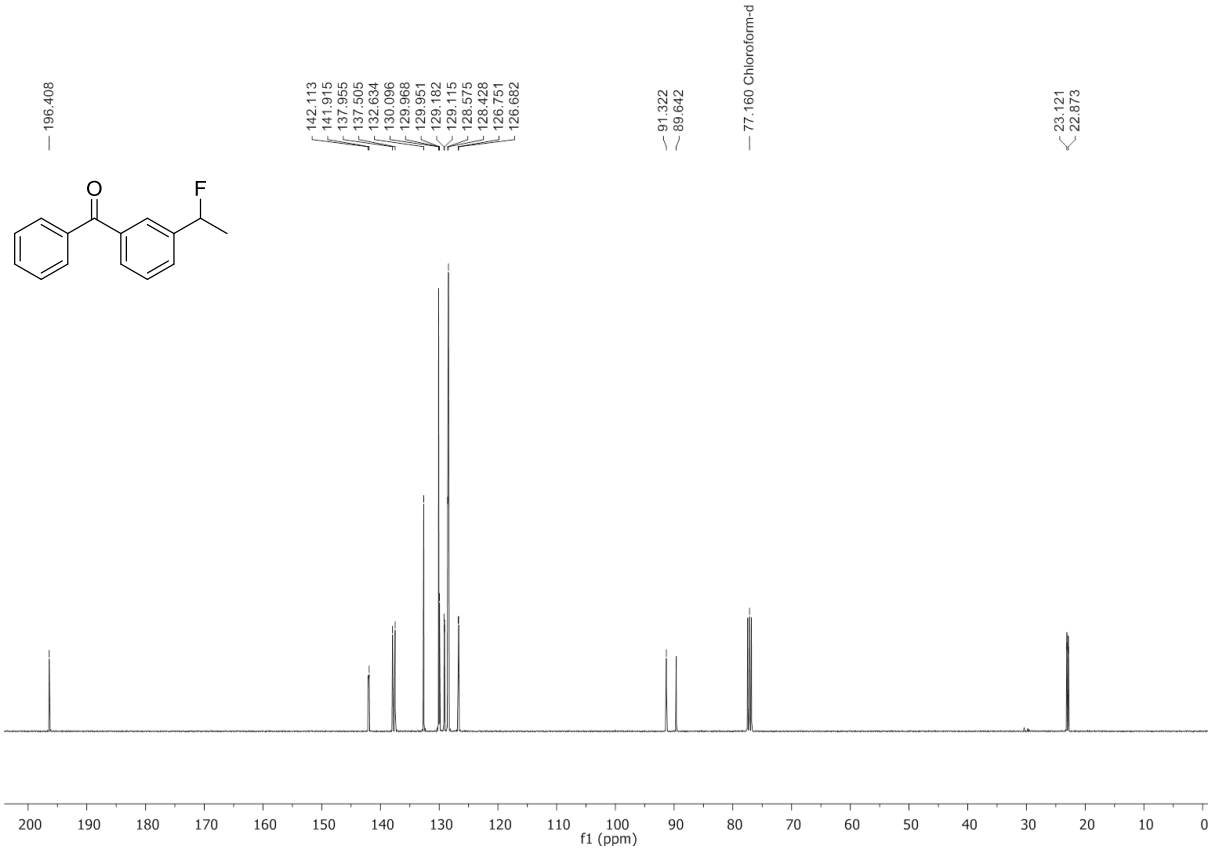


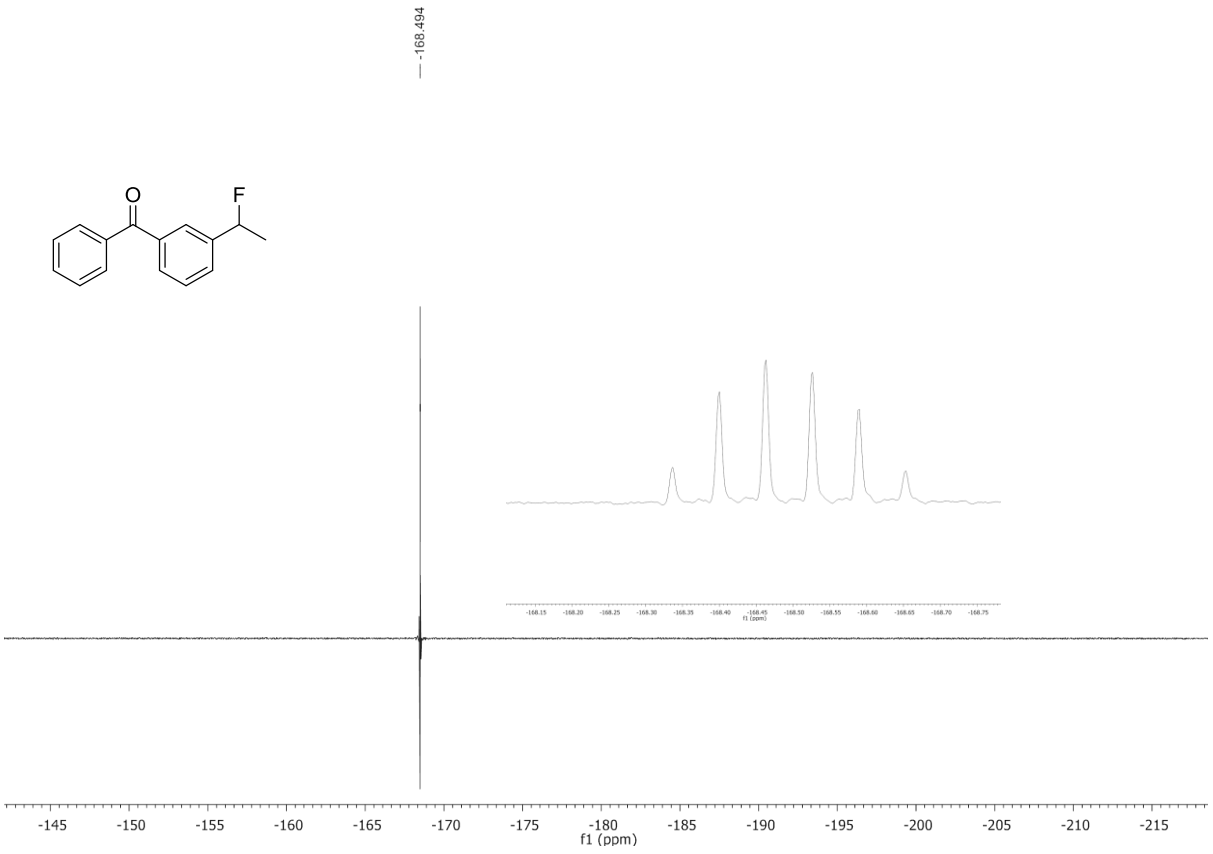




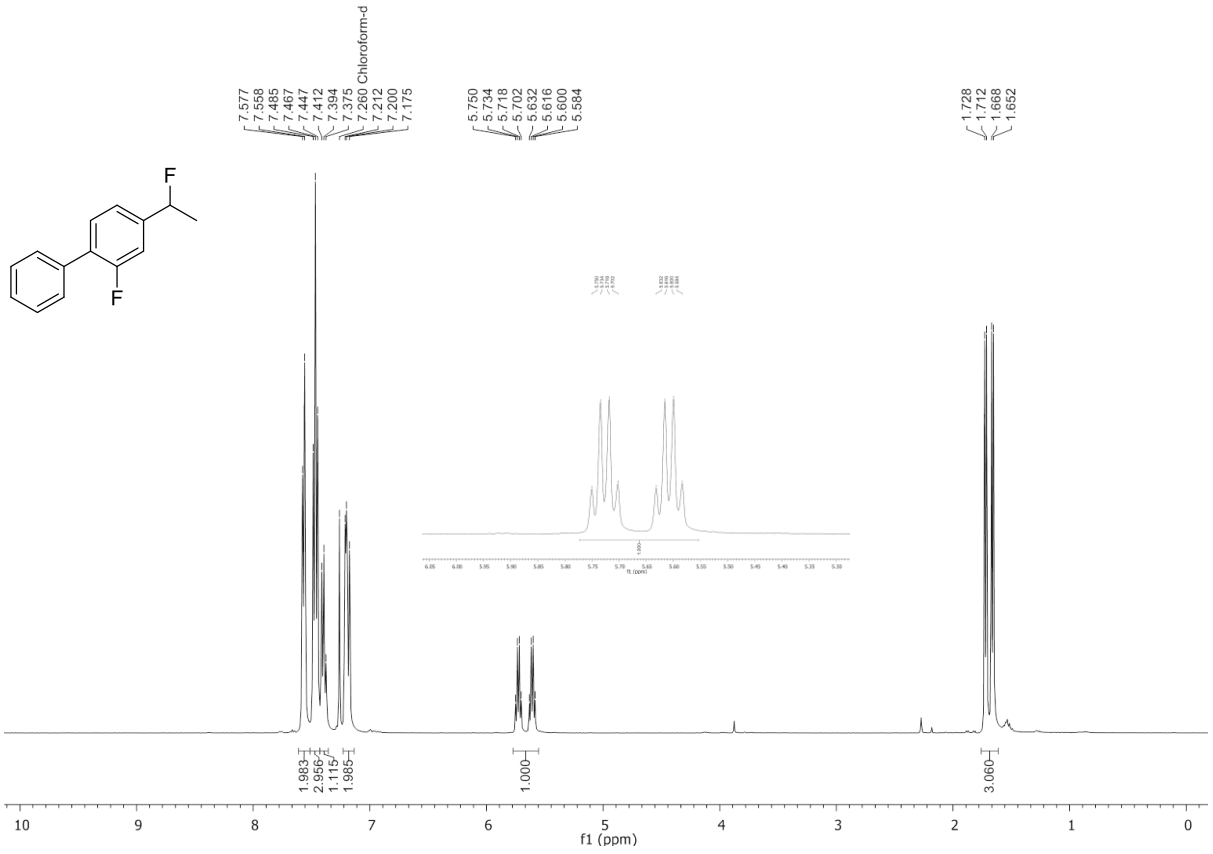
(3-(1-fluoroethyl)phenyl)(phenyl)methanone **95a**

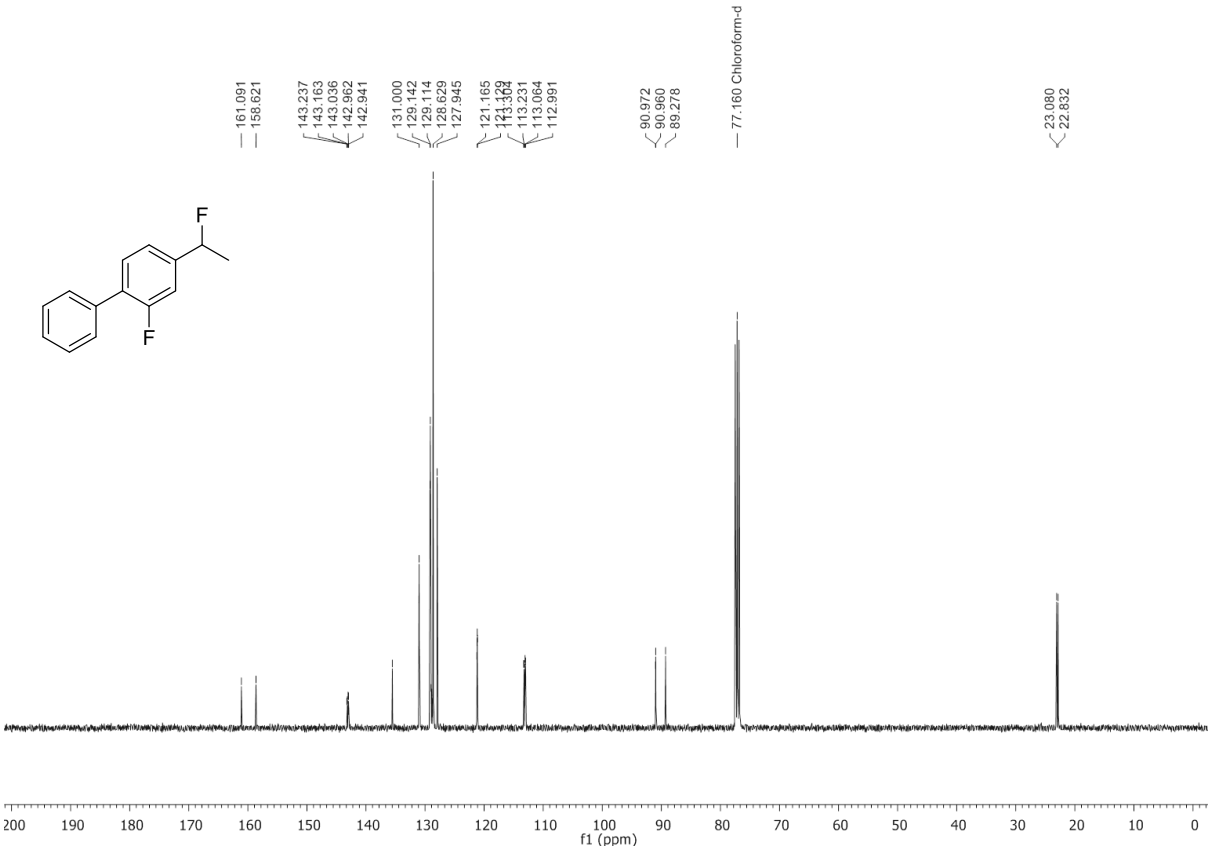


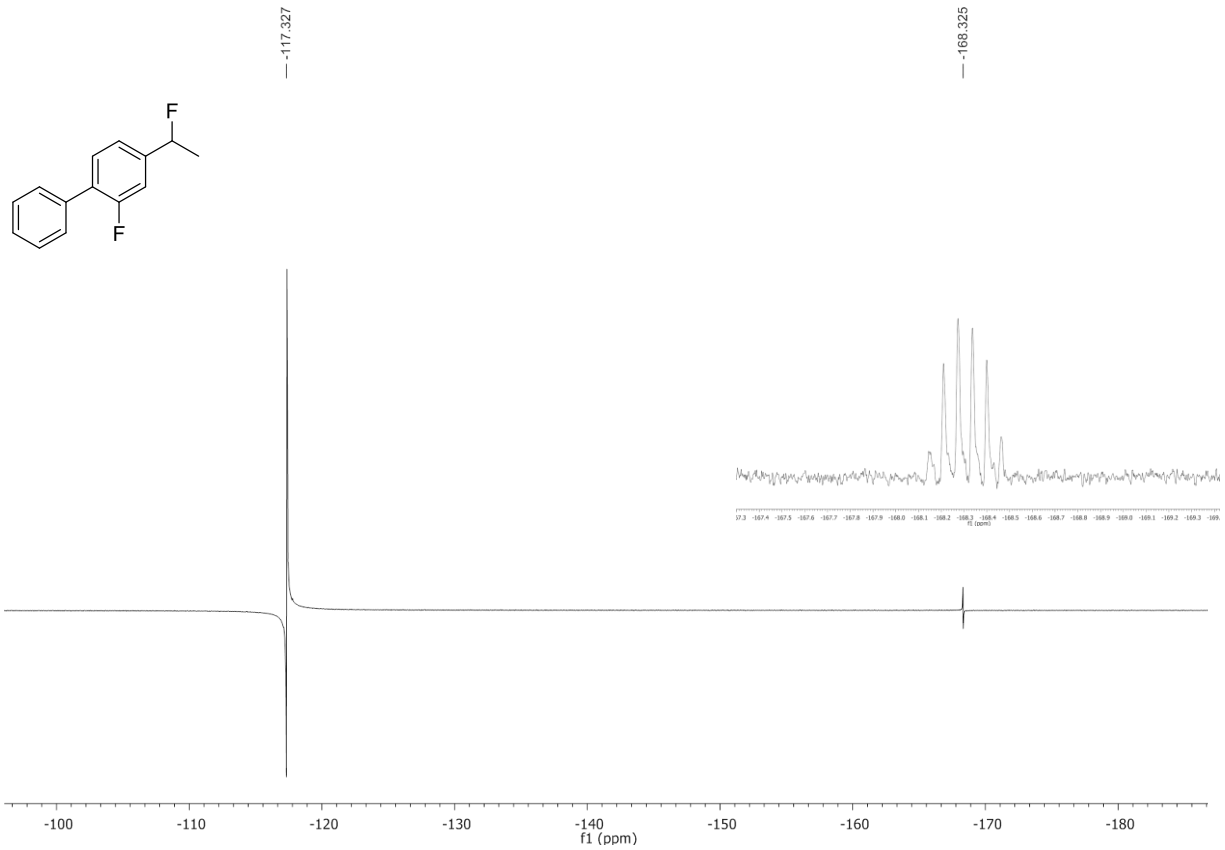

196.408
142.113
141.915
137.955
137.505
132.634
130.096
129.968
129.951
129.182
129.115
128.575
128.428
126.751
126.682
91.322
89.642
77.160 Chloroform-d
23.121
22.873
O
F
f1 (ppm)


-168.494
O
F
f1 (ppm)

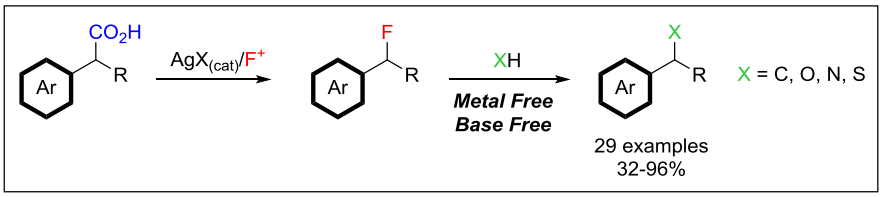
2-fluoro-4-(1-fluoroethyl)-1,1'-biphenyl **96a**






-117.327
-168.325
F
F
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

Chapter 4 – Decarboxylative Benzylic Activation: A Novel Mode of Reactivity Allows Access to C–C and C–Het Bonds

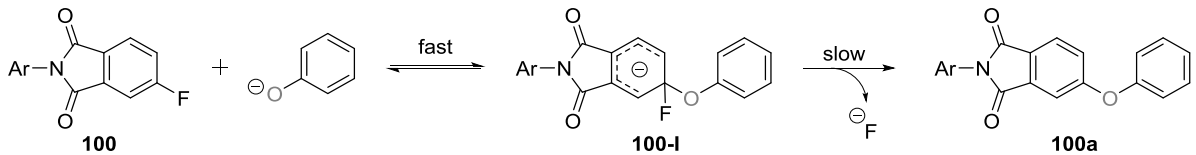


4.1. INTRODUCTION

Carbon-fluorine bonds are among the strongest single covalent bonds in organic chemistry.[103] Fluorine is the most electronegative atom in the periodic table and as a result the C–F bond is highly polarised with a substantial ionic character, however unlike other electronegative atoms (e.g. N and O) the non-bonding electrons on fluorine are held tightly to the nucleus and are largely inaccessible to hydrogen-bonding. Moreover, the poor polarisability of the fluorine atom means that direct displacement of fluoride is difficult making it a poor leaving group particularly in S_N2 reactions.[237] Despite these limiting factors a number of examples of C–F bond functionalisation have been reported and are discussed in the following sections.

4.1.1. Substitution at C(sp^2) centres

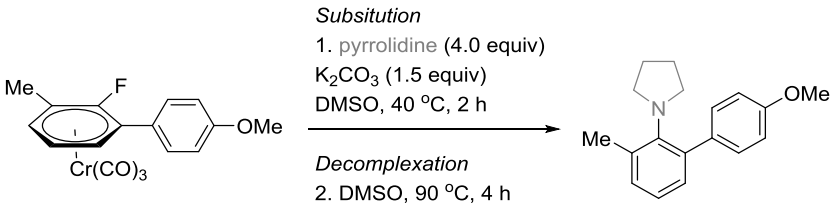
Nucleophilic aromatic substitution (S_NAr) is the most commonly encountered example of C–F bond substitution. The reaction mechanism involves two-steps, addition of a nucleophile to the electro-positive carbon *ipso* to the fluorine, then irreversible elimination of the fluoride which is the rate-determining step of the reaction (Scheme 110).[237] Addition-elimination reactions are common with fluorinated aromatics, the high electronegativity of fluorine helps to stabilise the Meisenheimer intermediate (**100-I**).



Scheme 110. Example of a nucleophilic aromatic substitution reaction with C–F bond cleavage.[237]

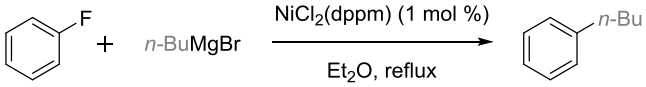
The rate of S_NAr reactions is enhanced by the addition of electron-withdrawing groups or using an electron-deficient (hetero)arene substrate; the reactivity can also be improved by π-complexation of the arene to a low-valent metal unit. The complexation of arenes to $Cr(CO)_3$, $[Mn(CO)_3]^+$, $[CpRu]^+$, $[Cp^*Ru]^+$ or $[CpFe]^+$ moieties activates the aromatic ring towards nucleophilic substitution due to the

electron-withdrawing ability of the metallic fragment.[238] Scheme 111 depicts the S_NAr of a fluorobenzene complexed to a tricarbonylchromium unit; substitution of the C–F bond in the corresponding free arene would be extremely sluggish requiring forcing conditions, however π-complexation permits reaction at ambient temperature.[239]



Scheme 111. Nucleophilic aromatic substitution of unactivated fluoroarenes can occur at lower temperatures (40 °C) via complexation of electron-withdrawing metal fragments such as $Cr(CO)_3$ which can be easily removed from the product by oxidative decomplexation (heating in DMSO or treating with MnO_2) or by UV irradiation.[239]

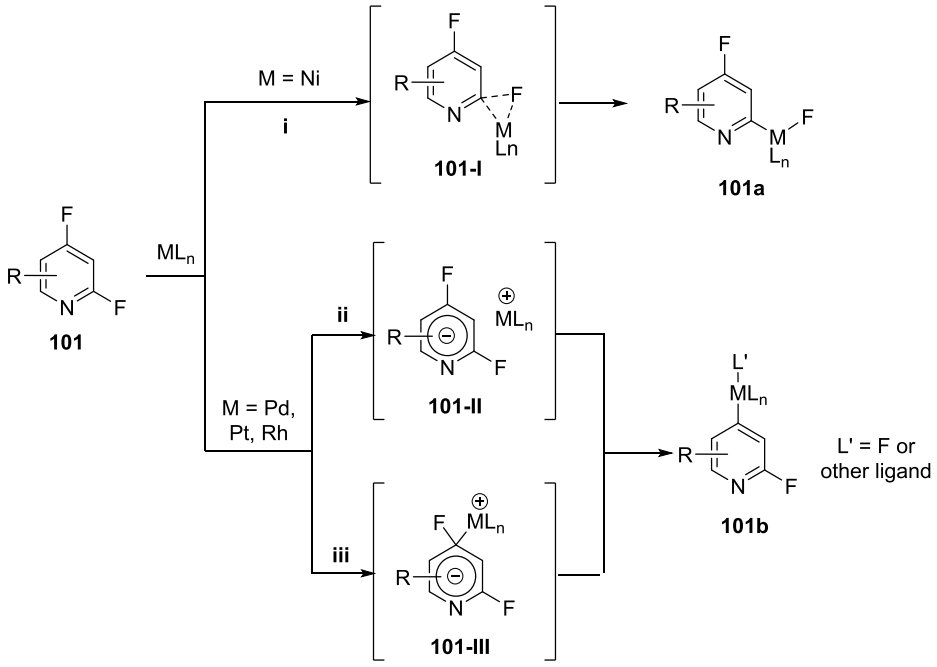
The ability to selectively functionalise aryl-halogen bonds using transition metal catalysed cross-coupling reactions has been well documented and exploited over the past few decades and has found an important place in medicinal chemistry, natural product synthesis and material science.[240] Pd and Ni catalysts are usually employed, with the initial step in the catalytic cycle being oxidative insertion of a zero-valent metal complex into the carbon–halogen bond. The bond dissociation energy of the C–Hal bond in mono-halobenzenes decreases down the group (C–F >> C–Cl > C–Br > C–I)[xiv] and thus due to the strength of the C–F bond (and to some extent the C–Cl bond) aryl bromides and iodides are most commonly used for the functionalisation of aromatic carbons. Accordingly, aryl fluorides are uncommon partners in cross-coupling reactions and selective C–F bond activation has received much attention since the first example of catalytic C–C bond formation involving $C(sp^2)$–F bond cleavage was reported by Tamao and Kumada in 1973 (Scheme 112).



Scheme 112. Nickel-catalysed Corriu-Kumada coupling of aryl fluorides involving the first example of $C(sp^2)$–F bond activation catalytic C–C bond formation.

Since this initial discovery that Ni can activate $C(sp^2)$–F bonds a number of different transition metals have also demonstrated this ability.[240,241] Interestingly, in the C–F activation of fluoropyridines (**101**) different metals exhibit differing regioselectivities (Ni = C2 selective, Pd, Pt, Rh = C4 selective) thus indicating that the oxidative insertion occurs by different mechanisms (Scheme 113).

[xiv] C_6H_5X: C–F = 127.2 kcal mol^{-1}; C–Cl = 97.1 kcal mol^{-1}; C–Br = 84 kcal mol^{-1}; C–I = 67 kcal mol^{-1}.[103]



Scheme 113. Plausible mechanisms for the C–H activation of fluoropyridines by various transition metals.[242]

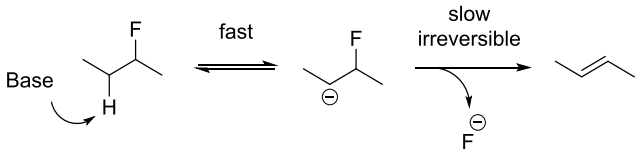
In this system, the plausible pathways for oxidative addition by metal complexes include: i) a concerted pathway involving the formation of a 3-centre-2-electron σ-complex (**101-I**); ii) electron-transfer from the electron-rich metal complex to the arene forming a tight ion pair (**101-II**); or iii) nucleophilic attack of the electron-rich metal complex to the arene via the Meisenheimer complex (**101-III**).

As determined by Perutz and Braun, in the presence of Ni(0) complexes, the metallation of poly or partially fluorinated pyridines occurs selectively at the C–F bond α to the nitrogen.[242] As a consequence, the authors conclude that the C2 regiochemistry gives indirect evidence for concerted oxidative insertion via a 3c-2e$^-$ pathway (i). Conversely, metallation at the C4 position indicates activation through electron transfer (ii) or S_NAr (iii) pathways; this is primarily favoured for period 5 and 6 transition metals due to steric reasons.[xv]

4.1.2. Substitution at C(sp^3) centres

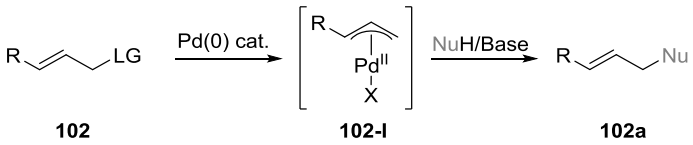
Although a poor leaving group, as observed for the case of S_NAr reactions the high electronegativity of fluorine means that it can stabilise anionic intermediates and thus fluoro organics are often observed to participate in E1cB elimination of fluoride under basic conditions (Scheme 114).[237]

[xv] Braun and Macgregor have noted the unusual C2 selective C–F activation of rhodium-boryl complexes.[243]



Scheme 114. Fluorine promotes E1cB reactions.

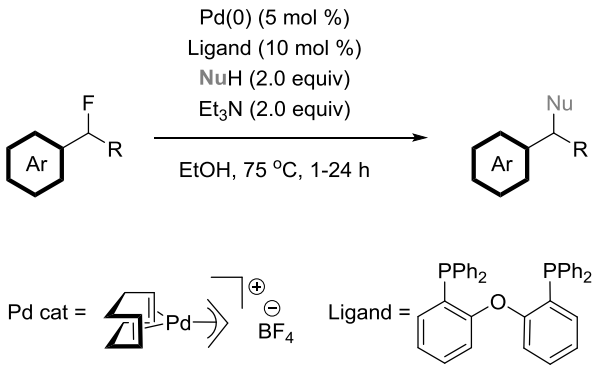
Allyl compounds with suitable leaving groups (**102**) can react with Pd salts to form well defined π-allyl palladium complexes (**102-I**). The reaction of these palladated complexes with nucleophiles was first demonstrated in 1965[244] by Tsuji and further developed in 1973[245] by Trost with the first asymmetric variant reported in 1977[246] (Scheme 115). Since the early pioneering work, the scope of the reaction has been greatly expanded to include allylations and benzylations employing a variety of different leaving groups, nucleophiles and metal catalysts.[247]



Scheme 115. Tsuji-Trost allylation of nucleophiles.

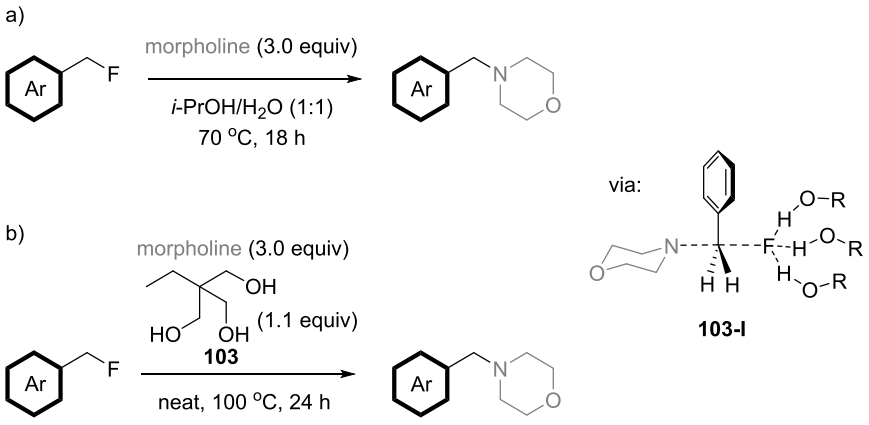
However, it was not until 2006 that the first example of metal-promoted C–F activation of allyl-fluorides by Pd and Pt complexes was reported by Togni and Hintermann.[248] Subsequently, a number of examples of Tsuji-Trost type allylations have been exhibited utilising fluoride as a leaving group.[249,250] Recently this approach was applied towards the Pd-catalysed coupling of benzylic fluorides; Brown and Gouverneur reported the benzylation of a variety of C, N, O and S based nucleophiles and the coupling of phenyl-boronic acid (Scheme 116).[251] The main disadvantages of this protocol include the use of a non-commercially available Pd catalyst and the preparation of starting materials via the substitution of brominated substrates using nucleophilic fluorides sources which can be difficult to handle; nevertheless more effective methods to access benzylic fluorides have been reported of late.[xvi]

[xvi] Discussed in Chapter 3.



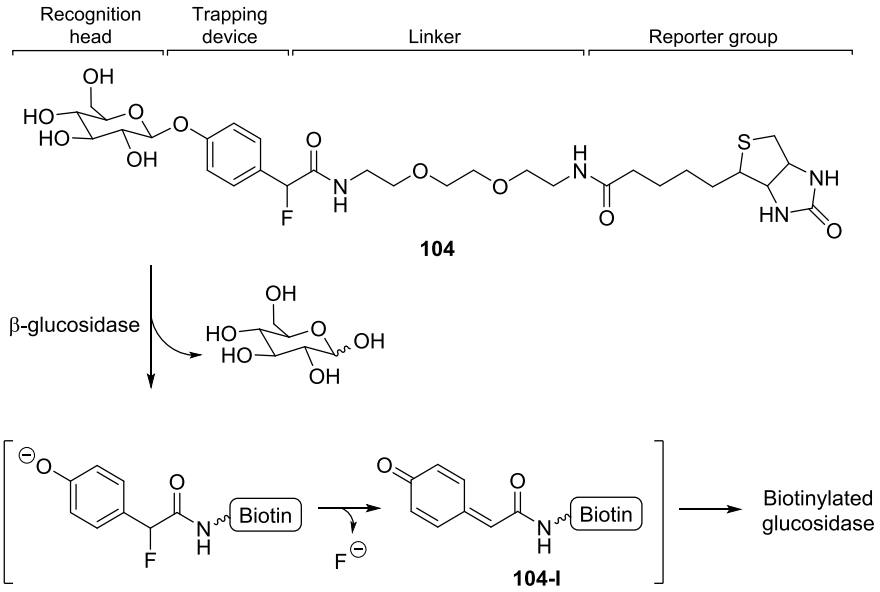
Scheme 116. Tsuji-Trost type cross-coupling of benzylic fluorides reported by Gouverneur *et al.*[251]

Transition-metal free routes to alkyl-fluorine bond substitution commonly exploit the Lewis basic nature of organic fluorine and employ Lewis (eg BF_3, BBr_3, $AlCl_3$, Me_3Al) or Brønsted (HX) acids or reactive species such as silyl- and carbo-cations.[240] The electron-pairs on organic fluorine are largely unavailable and thus strongly coordinating or highly reactive species are generally required to activate the C–F bond towards substitution. Accordingly, fluorine is also reported to be a poor hydrogen bond donor;[252] however, this notion primarily arose from analysis of crystallographic data and recently there has been increasing spectroscopic[253] and computational[254] evidence to suggest the existence of H-bonds to organofluorines in solution.[255,256] Taking this new evidence into account, in addition to the high solvation energy of fluoride in water (24 kcal mol^{-1}),[257] Paquin and co-workers successfully investigated the ability of H-bond donor solvents to activate alkyl fluoride bonds towards nucleophilic substitution (Scheme 117).[255] Computational studies showed that unlike the traditional cases of acid or cation promoted C(sp^3)–F activation (which follows a S_N1 mechanism), the H-bond donor assisted substitution occurs via a bi-molecular transition state (**103-I**) involving the coordination of 3 H-bonds to water (or *i*-PrOH or DMF). Furthermore, triol **103** was shown to promote substitution in solvent-free conditions at elevated temperatures (Scheme 117b).[258]



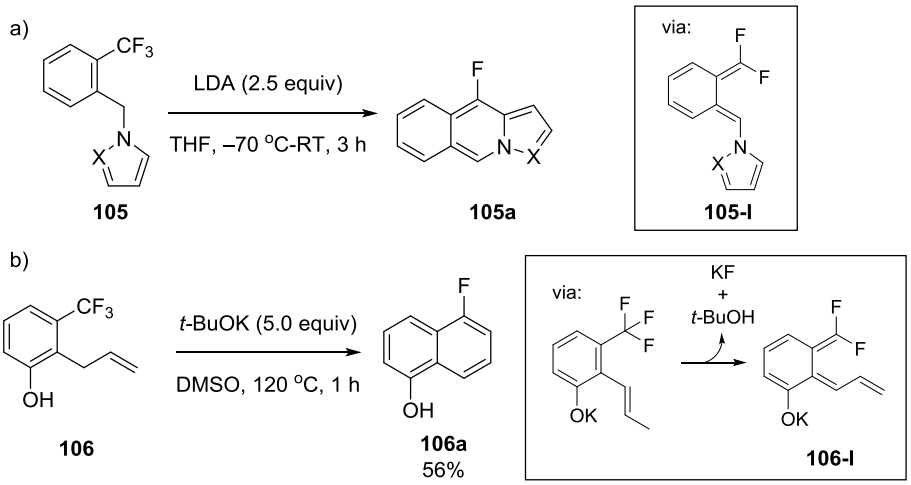
Scheme 117. Alcohol promoted nucleophilic substitution of benzylic fluorides reported by Paquin *et al.*[255,258]

Danzin and Lo showed that the *p*-glycosylated benzylic fluorides (e.g. **104,** Scheme 118) could be used as an activity probe for glycosidases.[259,260] The suicide-substrate **104** was designed to eliminate fluoride after enzymatic cleavage of the glycosyl ether, resulting in a reactive quinone methide **104-I** that subsequently reacts with a nucleophilic cysteine residue resulting in biotinylation of the enzyme.[261]



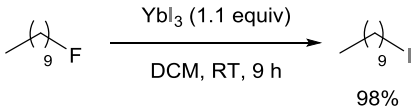
Scheme 118. Benzylic fluoride based glucosidase activity probe **104**.[259,260]

In a similar vein, reactive difluorinated quinone methide type intermediates (**105-I** and **106-I**) can be accessed in the presence of base from benzotrifluoride substrates such as **105** and **106**. Trifluoromethyl groups attached to π-systems have the ability to undergo negative hyperconjugation, meaning that these difluorinated quinone methide intermediates (e.g. **105-I** and **106-I**) are accessible but the ease at which depends upon the nature of the nearby functional groups. Kiselyov, demonstrated that deprotonation of acidic benzylic protons using a strong base (LDA) allows direct access to the reactive intermediates like **105-I** at low temperatures (Scheme 119a); subsequent cyclisation results in partially fluorinated heterocycles (e.g. **105a**).[262] However, substrate **106** is less activated towards difluorinated quinone methide formation and requires more forcing temperatures to promote formation of the partially fluorinated naphthols (Scheme 119b).[263]



Scheme 119. Base mediated activation of trifluoromethyl groups.[262,263]

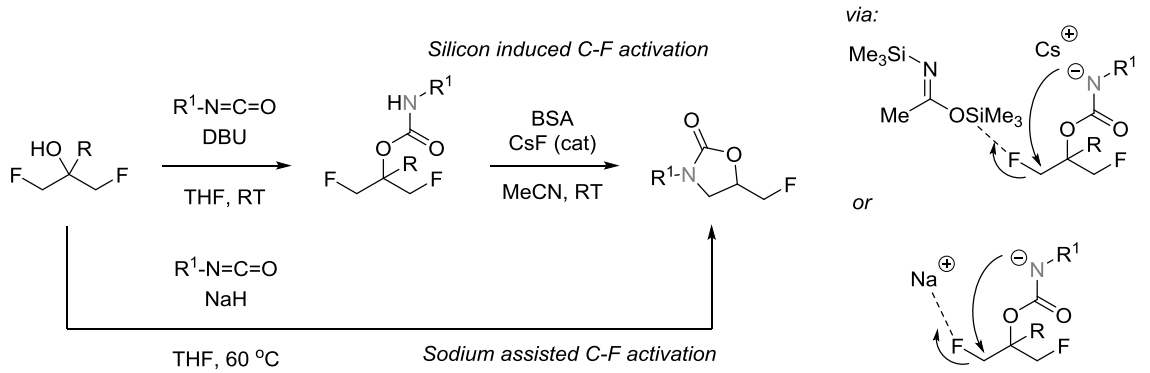
Aforementioned, the manipulation of unactivated C(sp^3)–F bonds usually requires the use of strong acids; in the case of strong Lewis acids these compounds are generally oxophilic in nature and this can present functional group tolerance issues and limit the scope of the nucleophile.[264] The Lewis acidity of lanthanide salts is well known[265] and increases from left to right in the periodic table with concomitant decrease in oxophilicity;[266] furthermore they form strong fluoride bonds.[267] With this consideration Hilmersson *et al.* recently reported the ytterbium mediated iodination of simple fluoro-aliphatics (Scheme 120).[264] Remarkably the reaction occurs at room temperature via S_N2 mechanism and is selective for C(sp^3)–F bonds with no reaction observed with aryl or alkenyl fluorides, or benzotrifluorides and exhibits only trace conversion with alkyl chlorides and bromides.



Scheme 120. Substitution of unactivated alkyl fluorides using YbI_3 reported by Hilmersson *et al.*[264]

Haufe and Shibata recently reported the C–F bond activation of unactivated aliphatic fluorides towards the synthesis of partially fluorinated oxazolidinones.[268] Their optimised protocol exploits the high Si–F binding affinity whereby the silyl base BSA is proposed to act as a base and Lewis acid in the presence of catalytic amounts of CsF to promote intramolecular cyclisation of the carbamate (preformed or formed *in situ* from carbamoylation with an isocyanate) onto the carbon of the C–F bond (Scheme 121). The cyclisation can also be facilitated with sodium bases such as NaOH and NaH however heating and prolonged reaction times are required. The use of KOH gave no conversion and KH was less effective than NaH with ~50% reduction in yield observed for the tandem carbamoylation /cyclisation. The authors propose that the C–F bond can be activated by the Na^+ ion.

Cation fluorine interactions are well studied[269] and alkali metal cations have been proposed to activate C−F bonds in similar transformations,[263] moreover, the increased lattice energy associated with NaF compared to KF warrants the enhanced reactivity observed with sodium salts.

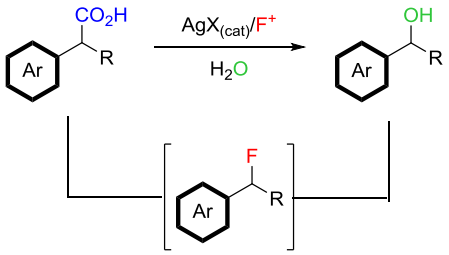


Scheme 121. Synthesis of partially fluorinated oxazolidinones reported by Haufe and Shibata involves C−F activation which can be facilitated by silicon or sodium.[268]

4.2. NUCLEOPHILIC SUBSTITUTION – ALCOHOL FORMATION (ONE POT)

4.2.1. Aims of the project

During the development of the Ag-catalysed decarboxylative fluorination protocol (discussed in Chapter 3) we noticed that the use of substrates bearing a carboxylic acid in the benzylic position resulted solely in oxygenated products (alcohol and ketone) and none of the desired fluorinated product was observed under the reaction conditions.



Scheme 122. Formal decarboxylative hydroxylation via decarboxylative fluorination and subsequent nucleophilic substitution.

Preliminary results suggested that the oxygenated products were not derived from direct reaction of oxygen or water with a benzylic radical or cationic intermediate but occurred via nucleophilic substitution of water on an intermediary benzylic fluoride (Scheme 122). By controlling the reaction time, the product distribution could be shifted in favour of fluoride or alcohol formation. This discovery was surprising as although Paquin and co-workers reported the nucleophilic substitution of benzylic fluorides with a number of nucleophiles, no substitution was observed with water after prolonged reaction times. Moreover, considering the increasing number of benzylic fluorination methodologies reported, investigation into the lability of the fluoride in the presence of water could be highly informative especially if this motif can be included in biologically relevant molecules.

The decarboxylation of phenyl acetic acids to yield oxygenated (or dimerisation) products has been well investigated; however the reported procedures can be limited by poor selectivity or the requirement of toxic metal salts.[270] Traditional routes to benzylic alcohols commonly involve hydride reduction of ketones or the nucleophilic addition of organometallic reagents (RMgX or ZnR_2) to aldehydes and due to the basic and nucleophilic nature of these reagents, anhydrous conditions are required and functional group incompatibility is inherent. Recently, a Pd-catalysed addition of boronic acids to aldehydes was reported.[271] This route offers a mild alternative to traditional methods but requires phosphine ligands, a chlorinated solvent and the use of boronic acids which although relatively environmentally benign, can be expensive. Therefore, a route which employs cheaper catalytic silver salts, aqueous reaction conditions and carboxylic acid substrates which are

inexpensive and readily available would be advantageous. A variety of phenylacetic acids are commercially available and can be readily α-functionalised using base and a variety of electrophiles. Furthermore, Thomas and co-workers recently published an Fe-catalysed carboxylation of styrenes.[234]

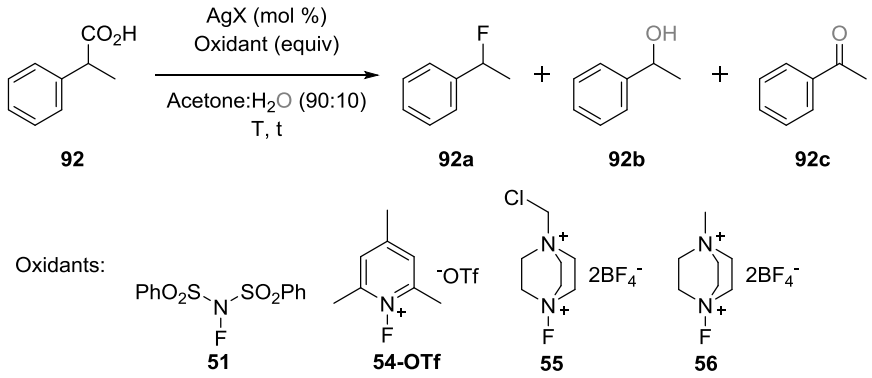
4.2.2. Optimisation

Initially when the reaction was carried out for 16 h, quantitative conversion of the acid (**92**) into the oxygenated products (**92b** and **92c**) was observed (Table 23, entry 1). However, when the reaction was stopped after 1 h a mixture of fluorinated (**92a**) and oxygenated (**92b** and **92c**) was obtained. (Table 23, entry 2). After reaction at 90 ^{o}C for 2 h, again no fluoride was observed with the major product being the alcohol (Table 23, entry 3). These three experiments indicate that the decarboxylation event is fast with no starting material remaining after 1 h and the product distribution gives indirect evidence that the reaction likely proceeds via decarboxylative fluorination to form **92a** which then undergoes nucleophilic substitution with H_2O to form **92b** (and subsequently **92c**).

When other commercially available sources of electrophilic fluorine were tested (Table 23, entries 4-7); the less oxidising reagents **51** and **54-OTf** were completely unreactive.[272] However, both Selectfluor (**55**) and the slightly less oxidising Selectfluor II (**56**) gave comparable results and thus the less expensive **55** was chosen to complete the optimisation. Next, the loading of **55** was investigated (Table 23, entries 7, 9, 11, 13, 14) with 1.15 equiv being the optimal amount. When the loading of **55** was decreased to 1.00 or 1.05 equiv the amount of over-oxidation product **92c** was not reduced and conversion occurred at a reduced rate (Table 23, entries 14 and 13, respectively). Similarly, decreasing the amount of silver from 20 to 10 mol % did not inhibit ketone formation and also slowed the reaction with 70% conversion observed after 3 h (Table 23, entries 9 & 10). Silver salts other than $AgNO_3$ were screened and all gave comparable results, however, due to the low price and ease of handling $AgNO_3$, was preferred.

The conditions shown in entry 11 were chosen as the optimal conditions for this substrate (**92**) giving quantitative conversion, 80% of the desired alcohol and least amount of by-products. To investigate the role of oxygen, the reaction was repeated under Schlenk conditions with a solvent mixture thoroughly degassed by 3 freeze-pump-thaw cycles. As shown in entry 12, this exclusion of oxygen resulted in no significant decrease in alcohol or ketone formation indicating that neither product arises from reaction with oxygen.

Table 23. Investigating the effect of oxidant and silver salt[a]

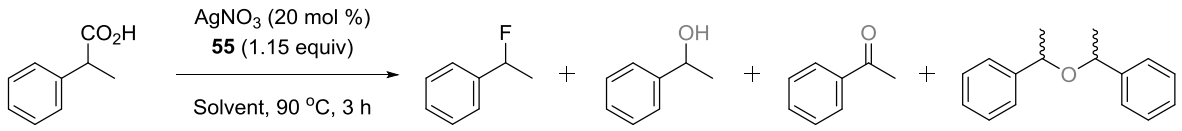


Entry	AgX (mol %)	Oxidant (equiv)	T (^{o}C)	t (h)	Product distribution (%)[b,c]			
					Conversion	F	OH	C=O
1	$AgNO_3$ (20)	**55** (1.50)	80	16	>99	0	77	13
2	$AgNO_3$ (20)	**55** (1.50)	80	1	>99	27	46	11
3	$AgNO_3$ (20)	**55** (1.50)	90	2	>99	0	70	13
4	$AgNO_3$ (20)	**51** (1.25)	90	2	0	0	0	0
5	$AgNO_3$ (20)	**54-OTf** (1.25)	90	2	0	0	0	0
6	$AgNO_3$ (20)	**56** (1.25)	90	2	96	0	75	8
7	$AgNO_3$ (20)	**55** (1.25)	90	2	97	0	77	9
8	$AgNO_3$ (20)	**55** (1.25)	90	3	97	0	71	9
9	$AgNO_3$ (20)	**55** (1.20)	90	2	92	0	71	11
10	$AgNO_3$ (10)	**55** (1.20)	90	2	69	0	53	11
11	$AgNO_3$ (20)	**55** (1.15)	90	3	>99	0	80	9
12[d]	$AgNO_3$ (20)	**55** (1.15)	90	3	>99	0	78	7
13	$AgNO_3$ (20)	**55** (1.05)	90	3	81	4	63	9
14	$AgNO_3$ (20)	**55** (1.00)	90	3	79	5	56	8
15	AgOAc (20)	**55** (1.15)	90	3	93	0	74	5
16	AgF (20)	**55** (1.15)	90	3	92	0	72	5
17	AgOTf (20)	**55** (1.15)	90	3	97	0	78	5

[a]Reaction conditions: unless otherwise stated, all reactions were carried out under air atmosphere. 0.3 mmol **92**, and the stated reagents in acetone:H_2O (95:5) (0.12 M) were heated in a 10 mL sealed vial for the stated time. [b]Yields calculated using mesitylene or trimethoxybenzene as the internal standard. [c]The remaining mass balance comprises a number of by-products in trace amounts. [d]Reaction carried out under Schlenk conditions using solvent degassed with 3 cycles of the freeze-pump-thaw method.

As previously discussed in Chapter 3, an acetone/H_2O mixture was identified as the best solvent system for the decarboxylative fluorination. Further optimisation of the decarboxylative hydroxylation reaction was carried out by investigating this solvent ratio. It was hoped that the reaction selectivity could be improved by suppressing the formation of by-products such as the ketone (**92c**), ether dimer (**92d**) amongst other unidentifiable trace products. Unsurprisingly, the amount of ether dimer increased when the amount of H_2O was lowered (Table 24, entry 1), this product presumably arises from nucleophilic substitution of **92b** on **92a**. Even though a 3:1 mixture of acetone:H_2O gave a better ratio of alcohol to ketone, the original 9:1 solvent mixture afforded the alcohol in a higher yield and gave the cleanest reaction out of all conditions tested (Table 24, entries, 3 and 2, respectively).

Table 24. Investigating the solvent ratio[a]



92 92a 92b 92c 92d

Entry	Solvent System	Product distribution (%)[b,c]					
		Conversion	F **92a**	OH **92b**	C=O **92c**	Ratio OH : C=O **92b : 92c**	Ether Dimer[d] **92d**
1[e]	Acetone:H_2O (95:5)	80	0	45	10	4.5:1.0	17
2	Acetone:H_2O (90:10)	>99	0	80	9	8.9:1.0	1
3	Acetone:H_2O (75:25)	>99	0	76	6	12.7:1.0	1
4	Acetone:H_2O (50:50)	>99	0	79	9	8.8:1.0	1
5	Acetone:H_2O (25:75)	98	0	74	15	4.9:1.0	1

[a]Reaction conditions: all reactions were carried out under air atmosphere. 0.3 mmol **92**, 20 mol % $AgNO_3$, 1.15 equiv **55,** in acetone:H_2O (0.12 M) were heated to 90 °C in a 10 mL sealed vial for 3 h. [b]Yields calculated using mesitylene or trimethoxybenzene as the internal standard. [c]The remaining mass balance comprises a number of by-products in trace amounts. 0.3 mmol acid, air atmosphere, 10 mL sealed vial. [d]Total of two diastereomers. [e]1.5 equiv of **55** used.

4.2.3. Substrate scope – General

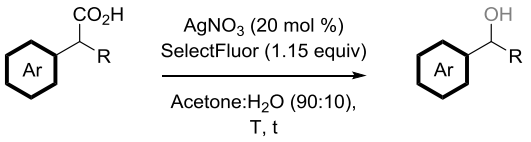
Once the optimal conditions for substrate **92** had been identified (Table 23, entry 11) the substrate scope was then investigated (Table 25). The reaction tolerates a variety of substituents on the aromatic side chain including: alkyl (**94b**, **107-108b**), fluoroalkyl (**110b**), aryl (**96b**, **98**-**99b**), ether (**93b**, **109b**), ketone (**95b**) and halides (**96b**, **110-113b**). A substituent α to the carboxylic acid is required; when the reaction was carried out with simple phenylacetic acid a complex mixture of products was obtained. Thus, different aliphatic substituents in the α position were investigated (methyl, *n*-butyl and benzyl); considering the highly oxidising conditions, benzylic positions (**94b**, **107b**) are tolerated despite reported oxidation[273] and fluorination[274] under similar circumstances.

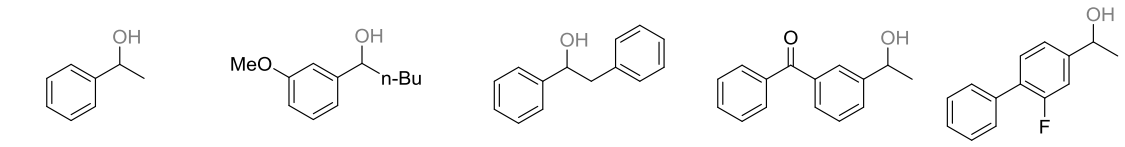
As previously discussed, current methods for benzyl alcohol formation involve the use of organometallic species or Pd catalysts, these routes would not tolerate some of the substituents reported herein such as ketone **95b** and halides **111-113b**. Moreover, alkyl and aryl fluorides are stable under the reaction conditions with no substitution of the C–F bond observed (**96b** and **110b**, respectively).

In terms of the electronic nature of the substituent, both electron donating (**93b**, **109b**) and withdrawing groups (**95-96b**, **110-113b**) are tolerated; however, there is a marked difference in reactivity. As discussed in Chapter 3, the decarboxylative fluorination scope is mildly affected by electronics, with the reaction conditions being broadly applicable to a number of substrates and any specific substrate optimisation was required to prevent the formation of the oxygenated products, not to promote overall conversion. On the other hand, the overall decarboxylative hydroxylation required significant optimisation for different substrates indicating that the nucleophilic substitution

step is sensitive to the electronic nature of the intermediate fluoride; but nonetheless a good range of substituents were tolerated and the reactivity follows a predictable trend with electron-deficient arenes requiring elevated temperatures and prolonged reaction times.

Table 25. Substrate scope for the one-pot decarboxylative hydroxylation of 2-phenylpropionic acids[a]





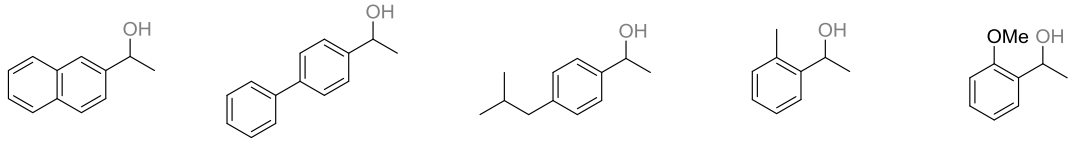
92b
(77%)[b] 50%
90 °C, 3 h

93b
68%[c]
90 °C, 3 h

94b
40%[c]
90 °C, 6 h

95b
68%[c]
90 °C, 6 h

96b
49%
90 °C, 5 h



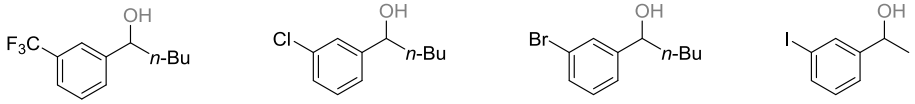
98b
58%
90 °C, 3 h

99b
60%
90 °C, 1 h

107b
74%
80 °C, 5 h

108b
64%
80 °C, 3 h

109b
76%
70 °C, 2 h



110b
32%[c]
90 °C, 16 h

111b
54%[c]
90 °C, 16 h

112b
36%[c]
90 °C, 16 h

113b
45%[c,d]
90 °C, 16 h

[a]Reaction conditions: all the reactions were carried out under an air atmosphere with 1.0 equiv of substrate, 20 mol % $AgNO_3$ and 1.15 equiv of Selectfluor (**55**) in 0.12 M solution of acetone/H_2O (90:10) at the stated temperature for the stated amount of time in a 20 mL sealed vial. Unless otherwise stated all reported yields are of the isolated product. [b]Yield was determined by ^1H NMR analysis using trimethoxybenzene as the internal standard. [c]1.25 equiv of **55** used. [d]30 mol % $AgNO_3$.

4.2.4. Substrate scope – Specific substrate optimisation

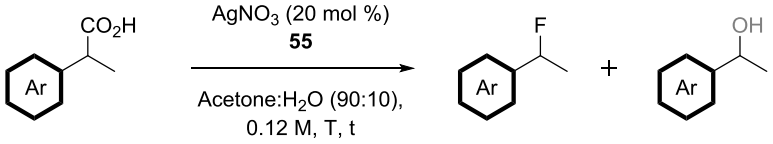
In this section, the optimisation of a number of specific substrates is discussed; the aim is to provide information for predicting the conditions required for a given substrate to react.

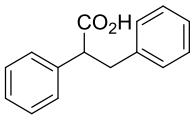
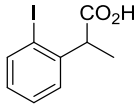
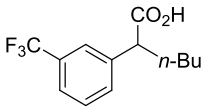
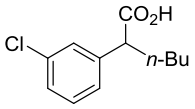
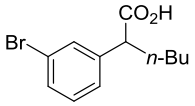
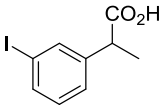
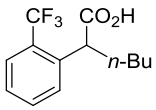
Some of the substrates detailed in Table 26 were not included in the final scope (Table 25) simply due to the fact that the desired alcohol was low yielding and/or there were large amounts of additional products formed which made purification difficult. Illustrative spectra are included in the supporting information.

The presence of an electron-withdrawing group on the aromatic ring reduces the reactivity of the substrate, this either occurs solely in the nucleophilic substitution step or also in the decarboxylation step to a lesser extent. The strongly electron-withdrawing trifluoromethyl group in *ortho* (**114**) gave good conversion of the acid over 3 h however conversion to alcohol was problematic (Table 26, entries 11-14). Initially, the temperature was increased to 100 ^{o}C (entry 12), but this resulted in reduced conversion of the acid, which could be attributed to decomposition of the oxidant at higher temperatures. Increasing the loading of oxidant from 1.15 equiv up to 1.50 equiv (Table 26, entries 11-14) slightly improved the conversion of the acid but resulted in increased by-product formation and consequently lower yields of fluoride and alcohol were realised. An improved yield of alcohol was found when the *m*-CF_3 substituted acid **111** was reacted for 16 h, however the reaction still resulted in unwanted by-product formation and incomplete conversion of the fluoride; the desired product was isolated in 32% yield (**110b**, Table 25).

Likewise in the case of substrates **97** and **113**, both compounds gave moderate to good conversion of the acid with 1.25 equiv of Selectfluor (Table 26, entries, 5 and 9) however the *meta* substituted compound **113** could be promoted towards alcohol formation after prolonged reaction times, the desired product was isolated in 45% yield (**113b**, Table 25). Other halide substituted acids were also tolerated; the chloro and bromo alcohols (**111b** and **112b**) were isolated in 54% and 36% yield after prolonged reaction times (Table 25). Analogous to the other electron-deficient substrates tested, the isolated yields of the products were moderate to low due to the formation of unwanted by products during the reaction course (Table 26, entries 7-8) .

Table 26 – Specific substrate optimisation[a]



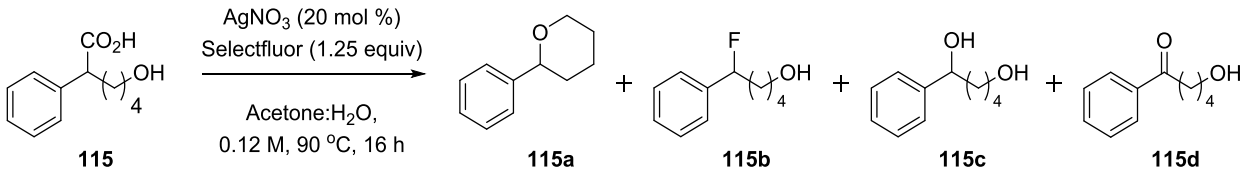
Entry	Substrate	Scale (mmol)	Selectfluor (equiv)	T (^{o}C)	t (h)	Product distribution				
						Conversion	F	OH	C=O	Other[e]
1[b]		0.3	1.15	90	3	95%	40%	36%	2%	Σ 13%
2[b]	**94**	0.3	1.25	90	4	97%	24%	50%	2%	Σ 19%
3[b]		0.3	1.15	80	1	62%	40%	4%	4%	Σ 20%
4[b]		0.3	1.15	90	1	55%	33%	6%	5%	Σ 19%
5[b]	**97**	0.3	1.25	90	3	66%	36%	7%	4%	Σ 17%
6[c]		1.0	1.25	90	16	n/a[d]	0.62	1.00	0.08	0.68
	110									
7[c]		1.0	1.25	90	16	n/a[d]	0.07	1.00	0.10	Σ 0.51
	111									
8[c]		1.0	1.25	90	16	n/a[d]	0.08	1.00	0.08	Σ 0.21
	112									
9[b]		0.3	1.25	90	16	45%	traces	44%	3%	Σ 3%
10[c]		1.0[d]	1.25	90	16	n/a[d]	0.05	1.00	0.09	traces
	113									
11[b]		0.3	1.15	90	3	90%	68%	7%	2%	Σ 16%
12[b]		0.3	1.15	100	3	78%	56%	9%	2%	Σ 8%
13[b]		0.3	1.25	90	3	93%	42%	10%	1%	Σ 34%
14[b]	**114**	0.3	1.50	90	3	98%	54%	6%	2%	Σ 31%

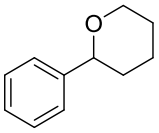
[a]Reaction conditions: unless otherwise stated all the reactions were carried out under an air atmosphere with 1.0 equiv of substrate, 20 mol % $AgNO_3$ and 1.15 equiv of **55** in 0.12 M solution of acetone/H_2O (90:10) at the stated temperature for the stated amount of time in a 20 mL sealed vial. [b]Yields calculated using ^{1}H NMR mesitylene or trimethoxybenzene as an internal standard. [c]Yields calculated as a relative ratio of all products observed by ^{1}H NMR. [d]No starting material was observed as a basic workup had been carried out. [e]Total amount of unidentifiable by-products.

Further optimisation could have been carried out for the substrates detailed in Table 26 in order to improve yield and minimise by-product formation however this was not pursued; in terms of synthetic applicability it is desirable to develop a methodology which is general and can be applied to a variety of substrates without too much deviation from the standard conditions. As a rule of thumb, the preferred reaction temperature seems to be 90 ^{o}C, with lower temperatures required for electron-rich substrates – for example the ortho-methoxy substituted **109b** gave the best result at 70 ^{o}C and the less electron-rich alkyl-substituted **107b** and **108b** gave better selectivity for the alcohol at 80 ^{o}C; under the standard reaction conditions (90 ^{o}C, 3 hours) a larger amount of ketone was produced for these substrates however the alcohol could still be obtained in good yield. The more electron-deficient the compound the slower both the decarboxylation and the nucleophilic substitution steps become. In order to improve the rate of both of these steps the amount of Selectfluor can be increased, however this can lead to off-cycle product formation, and moreover if this measure does not significantly improve the decarboxylation rate any alcohol that is formed can be subsequently oxidised to the ketone. In this instance it seems best to increase the loading of catalyst to accelerate decarboxylation and hence quickly reducing the amount of oxidant present in the reaction media to limit over oxidation.

Substituted tetrahydrofurans and tetrahydropyrans are frequently found in many cyclic ether antibiotics and other biologically active natural products.[275] Current routes to these motifs commonly involve (Brønsted[276] or Lewis[277]) acid catalysed hydroalkoxylation of alkenes; however alternative routes have been reported involving photochemical cyclisation[278] or Fe-catalysed cross-coupling to lithiated or magnesiated arenes.[279] In Table 27 some preliminary results for the intramolecular decarboxylative cyclisation of **115** are shown. Two different solvent ratios were tested over 16 hours, with around 10% of the desired product (**115a**) being observed in both cases. Unreacted starting material could be detected but the amount could not be elucidated by ^{1}H NMR analysis due to signal overlap; furthermore, uncyclised alcohol **115c** was observed as the major product.

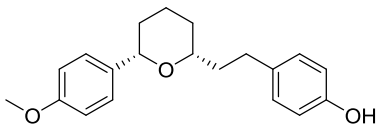
Table 27. Intramolecular hydroxylation optimisation[a]



Entry	Acetone:H_2O (ratio)	Product distribution (%)[b]					
		SM		F	OH	C=O	Other[d]
1	90:10	obs.[c]	11	0	34	4	5
2	95:5	obs.[c]	10	0	23	5	8

[a]Reaction conditions: all the reactions were carried out under an air atmosphere with 1.0 equiv of **115**, 20 mol % $AgNO_3$ and 1.15 equiv of **55** in 0.12 M solution at 90 °C in a 20 mL sealed vial. [b]Yields calculated using ^{1}H NMR and trimethoxybenzene as an internal standard. [c]Due to overlapping peaks the yield could not be accurately determined. [d]Total amount of unidentifiable by-products.

Decreasing the amount of H_2O in the reaction media did not help to promote cyclisation of the intermediate fluoride **115b** to give cyclic ether **115a**. As previously observed (cf. Table 27, entries 1 and 2) decreasing the amount of H_2O below 10% can in fact reduce overall conversion. To promote conversion, the loading of catalyst could be increased or alternatively an electron-donating group could be included on the ring, this approach may then present a route to the natural product (-)-Centrolobine (Figure 12). A more prudent approach to favour cyclisation maybe to utilise the Thorpe-Ingold effect[280] or to shorten the carbon chain of the pendant alcohol; alternatively, the reaction conditions for fluoride formation could be optimised, and then on isolation of **115b** the cyclisation could be carried out under anhydrous condition.[xvii]



(-)-Centrolobine

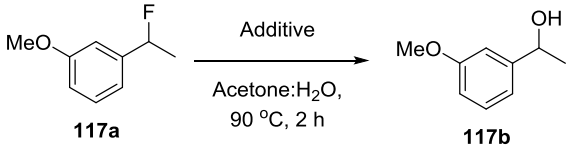
Figure 12. Cyclic ether natural product (-)-Centrolobine isolate from the heartwood of *Centrolobium robustum* from the stem of *Brosinum potabile*[281].

[xvii] Nucleophilic substitution of isolated benzylic fluorides will be discussed in Section 4.3.

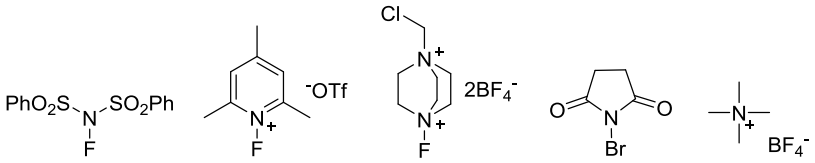
4.2.5. Mechanistic investigation

Table 28 details a number of different additives which were tested in order to better understand the mechanism of nucleophilic substitution in this system.

Table 28. Investigating the role of additives on the hydroxylation of **117a**[a]



117a **117b**



51 **54-OTf** **55** **118** **119**

Entry	Additive (mol %)	Product distribution (%)[b]			
		Conversion	OH **117b**	C=O **117c**	Ether Dimer **117d**
1	none		No reaction		
2	**55** (20)	>99	>99	0	0
3	**55** (25)	>99	82	0	0
4	**54-OTf** (20)	18	18	0	0
5	**51** (20)	7	7	0	0
6	**118** (20)	>99	Complex mixture inc. 9 % OH		
7	**119** (20)	0	0	0	0
8	$NaBF_4$ (20)	0	0	0	0
9	CsF (20)	0	0	0	0
10	H_3PO_4 (100)	>99	53	0	21
11	BiF_3 (25)	>99	57	0	28
12	$In(OTf)_3$ (8)	>99	30	0	48
13	$Zn(OTf)_2$ (25)	>99	34	0	45
14	SiO_2 (25)	0	0	0	0
15	Al_2O_3[b] (25)	>99	98	0	0
16	$MgSO_4$ (25)	0	0	0	0
17	$FeCl_3.6H_2O$ (25)	>99	80	0	0

[a]Reaction conditions: all the reactions were carried out under an air atmosphere with 0.1 mmol of **117a**, and the stated amounts of additives in 0.12 M solution at 90 °C for 2 h in a 10 mL sealed vial. [b]Yields calculated using ^{1}H NMR mesitylene as an internal standard internal standard.[c] Neutral Al_2O_3.

No conversion is observed when the fluoride is simply heated in an aqueous solution overnight (Table 28, entry 1).The optimal amount of Selectfluor required is 20 mol % (Table 28, entry 2) with an increase to 25 mol % causing by-product formation and consequently a reduced yield of alcohol (Table 28, entry 3). When other less oxidising sources of electrophilic fluorine were tested a significant decrease in conversion was observed which is consistent with their decreasing oxidation potential (Table 28, entries 4 and 5).[272] NBS (**118**) was also shown to facilitate conversion but its use resulted in a mixture of products which included 9% alcohol; this complex mixture may arise from

the presence of strong acid in the sample (Table 28, entry 6). The use of ammonium, tetrafluoroborate and fluoride sources resulted in no conversion thus ruling out the participation of these species in the reaction (Table 28, entries 7-9).

Aqueous solutions of Selectfluor exhibit a pH of ~3; this acidity is also exhibited in freshly recrystallised samples. The decomposition of Selectfluor in water is noted on the MSDS sheet;[282] furthermore, Stavber and Zupan have shown that the active fluorine content of Selectfluor in aqueous solution decreases by 4% over 24 h at ambient temperature, and 11% over 6 h when heated to 54 ^{o}C.[283] The mechanism of decomposition is as yet unknown but may result from fluorination of water yielding hypofluorous acid which rapidly decomposes to HF and O_2.[284] However, it has also been suggested that in some transformations, Selectfluor can act as a Lewis acid[285] and due to the observation in this system that both Brønsted and Lewis acids can effect conversion (Table 28, entries 10-17), neither role can be ruled out, at this time.

4.2.6. Conclusions

To summarise, an operationally simple procedure for the preparation of benzylic alcohols from carboxylic acids is presented. The reaction utilises an inexpensive metal catalyst and oxidant, and is carried out under aqueous conditions thus no exclusion of oxygen or moisture is necessary. The starting materials are stable and readily available from commercial sources via α-functionalisation of phenyl acetic acids or obtained via facile Fe-catalysed carboxylation of styrenes.[234]

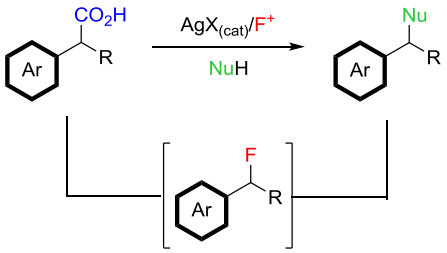
The reaction proceeds via decarboxylative formation of a fluoride intermediate which undergoes nucleophilic substitution with water. The reaction is facilitated by Selectfluor which acts as either a Brønsted or Lewis acid, as indicated by reaction of the isolated fluoride with suitable sources of acid. Investigation of the substrate scope indicates that a variety of substituents are tolerated in the reaction including those which may cause chemoselectivity issues in current routes to benzylic alcohol formation (bromine, iodine, ketone etc.). The nucleophilic substitution step seems very dependent upon electronics with electron-deficient substrates requiring longer reaction time and increased loading of catalyst or oxidant to increase reaction rate.[xviii] Nonetheless, conditions to afford good yields of untested substrates should be possible as the reactivity shows predictable trends based on the electronic nature of the substituents.

[xviii] A correlation between reactivity and electronics can be observed. A formal Hammett plot has not been carried out, however the apparent rate acceleration in the presence of electron-donating groups indicates a build-up of positive charge during the transition state and that the nucleophilic substitution step would exhibit a negative ρ value. The mechanism of the nucleophilic substitution step will be discussed further in Section 4.3.6.

4.3. NUCLEOPHILIC SUBSTITUTION – OTHER NUCLEOPHILES

4.3.1. Aims of the project

The one-pot decarboxylative hydroxylation methodology provided valuable insight into the reactivity of benzylic fluorides in the presence of Selectfluor or sources of acid. Following on from this the next step was to exploit the reactivity of this system towards new bond forming reactions (Scheme 123) and to gain greater insight into the mechanisms permitting substitution in this system.

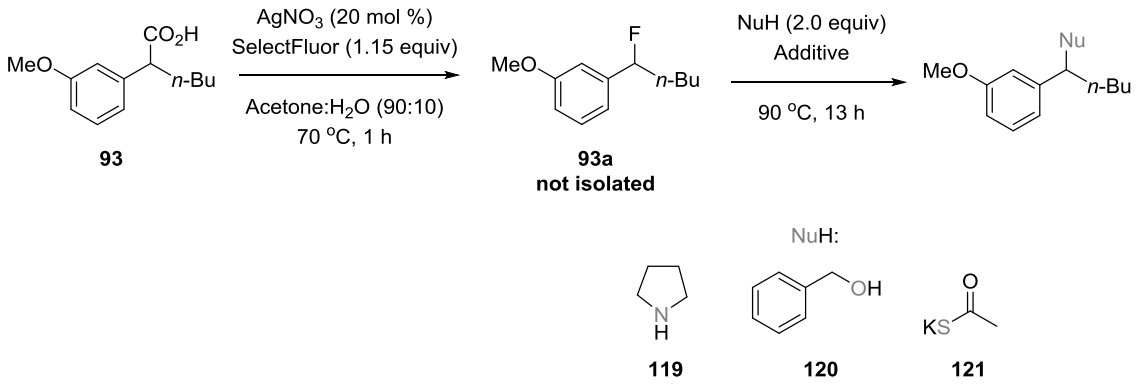


Scheme 123. Decarboxylative benzylic activation towards the formation of new C–C and C–Het bonds.

Paquin *et al.* showed that simple 1-fluoromethyl benzenes can react with nucleophiles in the presence of hydrogen-bond donor solvents over prolonged reaction times, however no reaction with water was observed.[255,258] Our initial investigations showed that nucleophilic substitution can occur in much shorter reaction times with water as the nucleophile (Table 28, entries 2 and 3), indicating that although the reaction temperature is in the same range as that utilised by Paquin, the reactivity of the fluoride is much greater in our system in the presence of Selectfluor. Furthermore, preliminary results showed that the model substrate used to investigate the effects of additives in the hydroxylation reaction (**117a,** Table 28) gave no conversion in the Pd-catalysed methodology presented by Gouverneur *et al*. Accordingly, a facile, metal-free route to form new C–C and C–Het bonds via substitution of benzylic fluorides would be of significant value, especially as there are a growing number of economical and efficient routes reported for their synthesis.

4.3.2. Optimisation (one pot)

Similar to allylic fluorides, benzylic fluorides can be unstable in the presence of strong acids or on boro-silicate glass when neat.[235] To negate any handling issues the scope of the nucleophilic substitution was initially tested in a one pot fashion. A large batch of the benzylic fluoride **93a** was prepared via fluorodecarboxylation and then several aliquots of the crude reaction mixture were placed into separate reaction vessels and heated with different additives and nucleophiles (Scheme 124).



Scheme 124. Attempted one-pot decarboxylative functionalisation with *O*, *N* and *S* based nucleophiles

Initially three nucleophiles were tested (pyrrolidine **119**, benzyl alcohol **120** and potassium thioacetate **121**) in combination with 6 Lewis acids (SelectFluor, BiF_3, $In(OTf)_3$, $FeCl_3.6H_2O$, $Sc(OTf)_3$, $Yb(OTf)_3$) including a control reaction without additional Lewis acid. In an attempt to absorb the water from the fluorodecarboxylation step, 200 wt % $MgSO_4$ was added in each reaction vessel. 21 reactions were carried out in total, with good (>60%) conversion observed in each reaction including the controls which only contained residual SelectFluor remaining from the first step. However none of the desired products were observed with substitution from water being the major product (alcohol **93b**). The outcome of these reactions indicated that $MgSO_4$ was not a competent desiccant at this temperature.

In the control reactions, the formation of the alcohol indicated that the residual Selectfluor remaining in the reaction media was enough to facilitate nucleophilic substitution and thus an exogenous Lewis acid was not necessarily required. Accordingly, the procedure was repeated with the same three nucleophiles (**119**, **120** and **121**) and the addition of different desiccants in an attempt to sequester the excess water. Flame dried $CuSO_4$, alumina, silica, activated charcoal and Montmorillonite K-10 were all tested and in each case a reduced amount of alcohol was observed, but unfortunately no traces of the desired products were detected. After this preliminary screen of 36 reactions, attention was focused on optimising the nucleophilic substitution from the isolated fluoride in order to prevent unwanted formation of the alcohol by-product.

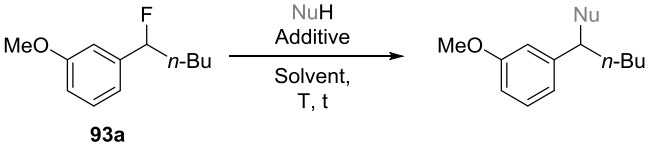
4.3.3. Optimisation (two pot)

Although unstable under certain circumstances, benzylic fluorides can be successfully isolated by carrying out final solvent removal after column chromatography in a PFA flask, plastic centrifuge tube or soda-lime glass vial. Furthermore, reactions in boro-silicate vials can be carried out providing that the fluoride is introduced to the reaction vessel in a solution.

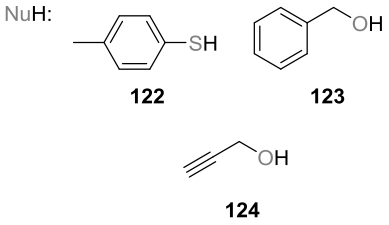
Initially, the optimisation of the nucleophilic substitution was carried out with 1-(1-fluoropentyl)-3-methoxybenzene (**93a**), Selectfluor (**55**) and *p*-methylbenzenethiol **122** (Table 29). The optimal

amount of nucleophile was found to be 2.0 equiv; lesser amounts of nucleophile resulted in the formation of by-products from reaction with residual water in the sample (Table 29, entries 1-3). As shown in Table 28, Brønsted acids can successfully mediate nucleophilic substitution of **29a** with water (Table 28, entry 10). Following on from this and with the assumption that Selectfluor may slowly decompose on heating to release acidic species, two sources of acid (**125** and **126**) were tested with nucleophiles other than water. Accordingly, 5 mol % PTSA (**126**) gave comparable results to 20 mol % Selectfluor (cf. Table 29, entries 3 and 7) in the nucleophilic substitution with **122**.

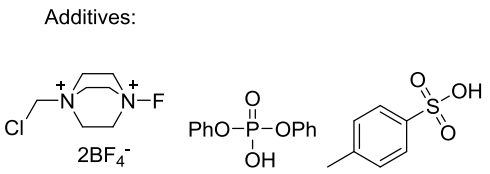
Table 29. Optimisation of the nucleophilic substitution of **93a** with *O*- and *S*- based nucleophiles[a]



93a



122 **123** **124**



55 **125** **126**

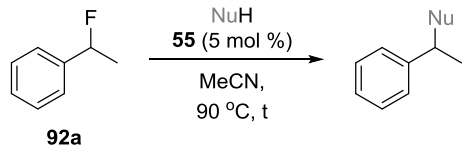
Entry	Nu**H** (equiv)	Solvent	Additive (mol %)	T (^{o}C)	Time	Product distribution (%)[b,c]			
						Conversion	Nu	OH	Ether Dimer
1	**122** (1.2)	Acetone	**55** (20)	90	2 h	>99	63	3	20
2	**122** (1.5)	Acetone	**55** (20)	90	2 h	>99	65	4	10
3	**122** (2.0)	Acetone	**55** (20)	90	2 h	>99	80	4	14
4	**122** (2.0)	Acetone	**55** (20)	70	2 h	>99	60	4	14
5	**122** (2.0)	Acetone	**55** (20)	50	2 h	30	0	9	0
6	**122** (2.0)	Acetone	**125** (5)	90	2 h	36	7	31	0
7	**122** (2.0)	Acetone	**126** (5)	90	2 h	>99	89	0	6
8	**122** (2.0)	Acetone	**126** (5)	70	2 h	8	0	6	0
9	**122** (2.0)	Acetone	**126** (5)	50	2 h	0	0	0	0
10	**123** (2.0)	Acetone	**126** (5)	90	2 h	32	18	10	0
11	**124** (2.0)	Acetone	**126** (5)	90	2 h	34	13	13	0
12	**123** (2.0)	Acetone	**55** (20)	90	2 h	>99	>99	0	0
13	**124** (2.0)	Acetone	**55** (20)	90	2 h	>99	88	12	0
14	**122** (2.0)	Acetone	**55** (20)	90	1 h	>99	74	2	5
15	**122** (2.0)	Acetone	**55** (5)	90	1 h	>99	73	2	8
16	**122** (2.0)	EtOAc	**55** (5)	90	30 min	trace	trace	0	0
17	**122** (2.0)	DMA	**55** (5)	90	30 min	trace	trace	0	0
18	**122** (2.0)	*t*-AmOH	**55** (5)	90	30 min	3	0	3	0
19	**122** (2.0)	Diglyme	**55** (5)	90	30 min	38	6	30	0
20	**122** (2.0)	MeCN	**55** (5)	90	30 min	>99	76	2	0

[a]Reaction conditions: all reactions were carried out in flame dried glassware, under Ar atmosphere, with 0.1 mmol of **93a** and the stated amounts of reagents and anhydrous solvents in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR using mesitylene as the internal standard. [c]Remaining mass balance attributed to small amounts of unidentifiable by-products.

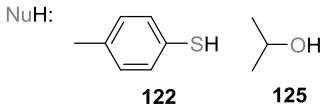
Consequently the optimisation was continued with both Selectfluor (**55**) and PTSA (**126**). On decreasing the temperature from 90 to 50 °C a slower conversion resulted with Selectfluor, however the reaction mediated by PTSA completely shut down at 70 °C (cf. Table 29, entries 3-5 and 7-9). Furthermore, a marked difference in reactivity was observed between **55** and **126** with more basic nucleophiles (**123** and **124**). For the acid catalysed reaction, only 30% conversion was observed with benzyl and propargyl alcohol (Table 29, entries 10 and 11), yet no decrease in reactivity was observed with Selectfluor (Table 29, entries 12 and 13) on comparison to the less basic sulfur-based nucleophile (Table 29, entry 3). This observation could indicate that the Brønsted acid and Selectfluor mediated reactions occur via different pathways, or at least the reaction in the presence of Selectfluor is not due to acidic species formed through a thermal decomposition pathway.

To find the optimal reaction conditions using **55**, the reaction time with **122** was decreased from 2 h to 1 h (Table 29, entries 3 and 14, respectively) with a slight decrease in desired thioether product but less ether dimer by-product observed. Decreasing the loading of **55** from 20 mol % to 5 mol % (Table 29, entries 14 and 15, respectively) had no detrimental effect on product yield. So far the reactions carried out with **122** as the nucleophile had resulted in good yields of the desired product but several low-yielding unidentifiable by-products; to investigate if cleaner conversion could be obtained using a different solvent system, a number of polar solvents were tested (Table 29, entries 16-20). When the reaction was carried out in MeCN over a reduced reaction time of 30 min (Table 29, entry 20) cleaner conversion to the thioether was observed with a major byproduct being the oxidised thioether (as confirmed by GC-MS analysis) and trace unidentifiable by-products. This observation indicated that the reaction in MeCN was occurring rapidly, during which the desired thioether product is quickly formed and then oxidised (likely by the residual Selectfluor in the reaction media). Consequently, MeCN was chosen as the optimal solvent as it permitted faster conversion than using acetone; however the reaction still seemed to lead to a number of un-identifiable by-products. A test reaction was carried out where substrate **93a** was heated under the reaction conditions in the absence of an exogenous nucleophile, this resulted in full conversion of fluoride to a complex mixture of products some of which seemed to arise from self-condensation of **93a** whereby the nucleophilic ring carbons on the anisole motif could be reacting with the activated benzylic fluoride. To test this hypothesis, **92a** was submitted to the optimised reaction conditions (5 mol % Selectfluor, MeCN, 90 °C, 30 min) as it does not have any functional groups on the aromatic ring which could activate it towards electrophilic aromatic substitution (Table 30). Accordingly, using benzylic fluoride **92a** gave clean, quantitative conversion to the thioether product (Table 30, entry 1) and therefore the remaining optimisation was carried out with this substrate (Table 30).

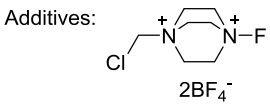
Table 30 – Optimisation of the nucleophilic substitution of **92a** with *O*- and *S*- based nucleophiles[a]



92a



122 **125**



55

Entry	NuH (equiv)	Time	Product distribution (%)[b]			
			Conversion	Nu	OH	Ether Dimer
1	**122** (2.0)	30 min	>99	>99	0	0
2	**122** (2.0)	15 min	>99	>99	0	0
3	**122** (1.2)	30 min	>99	86	4	5
4	**125** (2.0)	15 min	66	64	2	0
5	**125** (2.0)	30 min	90	63	10	0
6	**125** (2.0)[c]	30 min	90	90	trace	0

[a]Reaction conditions: all reactions were carried out in flame dried glassware, under Ar atmosphere, with 0.1 mmol of **92a**, 5 mol % **55** and the stated amount of nucleophile in anhydrous MeCN in a 10 mL sealed vial. [b]Yields determined by ^{1}H NMR using trimethoxybenzene as the internal standard. [c]Dried over CaH_2 and distilled prior to use.

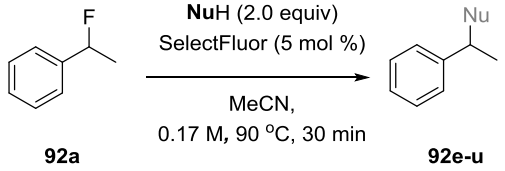
Even using the new system, the optimal amount of nucleophile was confirmed to be 2.0 equiv with 1.2 equiv of the *S*-based nucleophile **122** leading to by-product formation from adventitious water (cf. Table 30, entries 1 and 3). Pleasingly, *O*-based nucleophiles was also amenable to reaction under these conditions with isopropanol (**125**) giving 66 % conversion in 15 minutes, longer reaction times (30 min) lead to increase in conversion but not yield, with the formation of the alcohol and other unidentifiable by-products occurring (Table 30, entries 4 and 5, respectively). When a sample of freshly distilled **125** was used, clean conversion to the desired product occurred in 90 % yield with no by-product formation and only unreacted starting material remaining (Table 30, entry 6). With longer reaction times, quantitative conversion with **125** would likely have been achieved and the reaction with **122** gave quantitative yield in only 15 minutes; however, reaction with 5 mol % catalyst for 30 minutes allowed excellent yields with both *O*- and *S*-based nucleophiles and was consequently chosen as the optimal reaction conditions (Table 30, entries 1 and 6).

4.3.4. Substrate scope

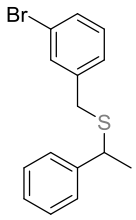
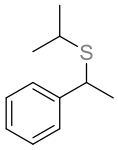
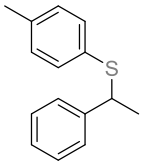
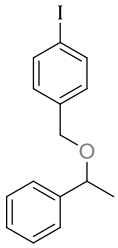
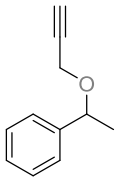
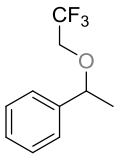
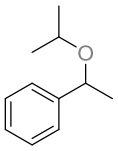
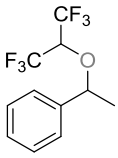
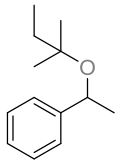
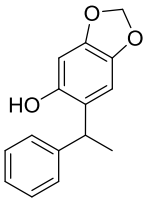
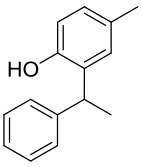
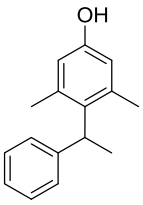
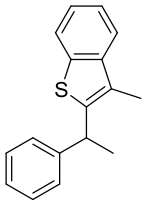
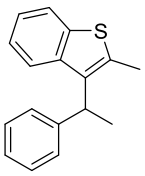
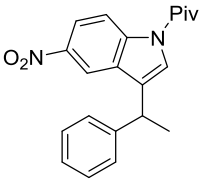
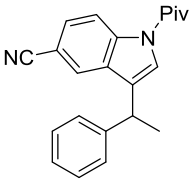
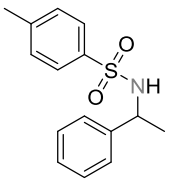
With high yielding conditions elucidated for **122 a**nd **125**, the scope of the reaction with 1-fluoroethylbenzene (**92a**) was investigated using different nucleophiles (Table 31). Sulfur based nucleophiles reacted in excellent yields (**92e-g**), similarly aliphatic alcohols were well tolerated (**92h-k**) with the electron-deficient 2,2,2-trifluroethanol (TFE) reacting in excellent yield without the

requirement for additional base (**92j**). As mentioned previously, reaction with isopropanol gave 90% of the desired product (**92k**), however the bulky *tert*-amyl alcohol failed to yield any product (**92m**); similarly the bulky and electron-deficient 1,1,1,3,3,3-hexafluoro-*iso*-propanol (HFIP) gave none of the desired substitution product (**92l**).

Table 31 – Substrate scope of the nucleophilic substitution of 1-fluoroethylbenzene **92a**



92a **92e-u**

					
(93%)[b] 77% **92e**	**(81%)[b,c]** **92f**	**(99%)[b] 96%** **92g**	**(99%)[b] 80%** **92h**	**(99%)[b,c,d]** **92i**	**(92%)[b,c,d]** **92j**
					
(90%)[b,c,d] **92k**	**0%** **92l**	**0%** **92m**	**(99%)[b] 85%** **92n**	**(73%)[b] 66%** **92o**	**(80%)[b] 82%** **95:5 (*p:o*)** **92p**
					
(56%)[b] 51% **92q**	**(81%)[b] 80%** **92r**	**(62%)[b] 51%** **92s**	**(54%)[b] 54%** **92t**	**(47%)[b,e,f]** **92u**	

[a]Reaction conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **92a** in a 0.17 M solution of MeCN, 5 mol % **55** and 2.0 equiv of nucleophile at 90 °C for 30 min in a 10 mL sealed vial. Unless otherwise states all yields correspond to the pure isolated product. [b]Yield was determined by ^{1}H NMR analysis using mesitylene or trimethoxybenzene as the internal standard. [c]This product was found to be volatile and could not be successfully isolated in appreciable yield. [d]Nucleophile was dried over CaH_2 and distilled prior to use. [e]This product co-eluted with unreacted starting material and could not be successfully separated after several attempts. [f]*tert*-butyl tosylcarbamate was used as the nucleophilie and the resulting product underwent Boc deprotection *in situ.*

Interestingly, the use of aromatic alcohols such as *para*-cresol (the oxygen analogue of **122**) gave only trace amounts of coupling through the oxygen, with the major product being substitution at the *ortho*-position (**92o**). Likewise, the use of more electron-rich phenols such as sesamol and 3,5-dimethylphenol resulted in substitution through nucleophilic ring carbon atoms (Table 31, **92n** and **92p**, respectively). Furthermore, the major regioisomer obtained with 3,5-dimethylphenol occurred via substitution at the more sterically hindered *para* position (**92p**; 95:5 *para:ortho*).

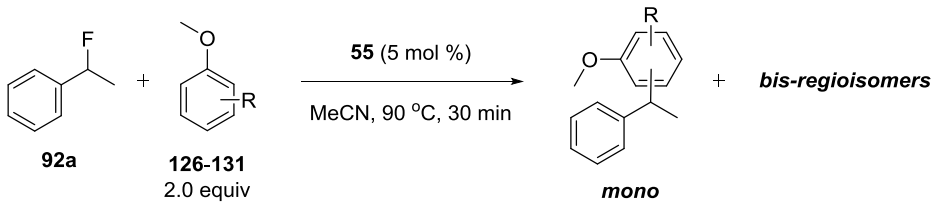
Other aromatic carbon-based nucleophiles were tested (**92q-t**); selective substitution of benzothiophenes could be obtained by using 3 or 2 methyl-substituted substrates (**92q** and **r**, respectively); in the absence of a blocking methyl group several mono- and bis-regioisomers were obtained. Remarkably, deactivated indoles gave good yield of coupling product despite the presence of strongly electron-withdrawing groups on the aromatic ring and nitrogen (**92s-t**). Substitution through a nitrogen atom was achieved using the extremely poor nucleophile *tert*-butyl tosylcarbamate, this substrate reacted then underwent *in situ N*-Boc deprotection to yield 92**u** in 47% yield.

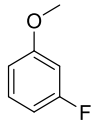
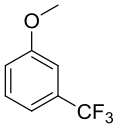
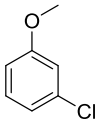
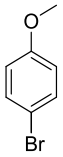
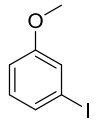
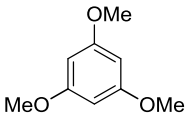
The substrate scope in Table 31 shows that not only can a variety of different *C*, *O*, *N*, and *S*-based nucleophiles be rapidly incorporated without the requirement of exogenous base, but the reactive nature of the benzylic fluoride allows for the use of some surprising nucleophiles, namely the electron-deficient TFE (**92j**), *N*-pivaloyl indoles (**92s-t**) and protected sulfonamides (**92u**). Moreover, as the reaction conditions are metal-free, a number of synthetically useful substituents and functional groups can be tolerated without regioselectivity issues including: bromo (**92e**), iodo (**92h**), alkynyl (**92i**), alcoholic (**92n-p**), nitro (**92s**), cyano (**92t**) and sulfonamide (**92u**) substituents

4.3.5. Other nucleophiles tested

Numerous other nucleophiles were screened under the reaction conditions detailed in Table 9 but were omitted from the final substrate scope due to poor regioselectivity or reactivity, without additional optimisation being carried out. The reactions were analysed by ^{1}H NMR using the resonance of the α-proton on the benzylic moiety to determine product distribution by comparing the shift to known or analogous compounds and further verified by GC-MS analysis. Data pertaining to the crude reaction mixtures are not included and the regiochemistry of the different isomers was not determined. The outcomes of these reactions are discussed below solely to provide information on the reactivity of the system.

Table 32. Attempted nucleophilic substitution of **92a** with different anisoles[a]



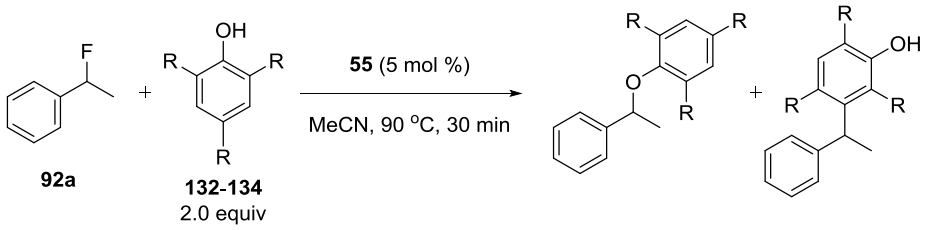
Entry	Substrate	Product Distribution[b]	Entry	Substrate	Product Distribution[b]
1	 **126**	>99% conversion 3 regioisomers major = 45%	5	 **129**	20% conversion no desired product products arising from H_2O
2	 **127**	>99% conversion 3 regioisomers major = 54%	6	 **130**	90% conversion 2 regioisomers = Σ 15% products arising from H_2O
3	 **128**	>99% conversion several mono and bis-regioisomers detected	7	 **131**	>99% conversion mono:bis 62% : 28% traces of tris

[a]Reaction conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **92a** in a 0.17 M solution of MeCN, 5 mol % **55** and 2.0 equiv of nucleophile (**126**-**131**) at 90 °C for 30 min in a 10 mL sealed vial. [b]Product distribution was determined by ^{1}H NMR analysis using mesitylene or trimethoxybenzene as the internal standard.

Table 32 details the reaction of **92a** with a number of anisoles. Initially different 3-substituted anisoles were tested in the hope that the additional substituent could prevent the formation of regioisomers by blocking reaction at the adjacent positions through steric and electronic effects. The use of 3-fluoro anisole (**126**) gave a mixture of 3-regiosiomers with the major detected in 45%, on switching to the larger chloro-substituent (**127**) improved selectivity for the major regioisomer was obtained however the reaction still remained largely unselective. It was hoped that the increased steric bulk of the iodine (**128**) would favour reaction at the least sterically hindered *ortho* position; on the contrary, the reaction was even more unselective with several mono and bis regio-isomers detected by GC-MS. Iodine is less inductively electron-withdrawing and more electron-donating by resonance than chlorine, which rationalises the formation of the other mono- and bis-substituted regioisomers. Following on from this, the more sterically bulky and electron-withdrawing 3-trifluoromethylanisole (**129**) was tested, however this substrate was too deactivated towards nucleophilic substitution and no desired product was formed. Halogens are *meta*-deactivating and 4-bromoanisole (**130**) reacted slowly resulting in preferential reaction of **92a** with adventitious water. Trimethoxybenzene (**131**) was successfully reacted to give 62% of the mono-substituted product and

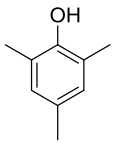
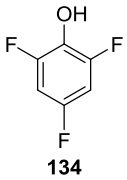
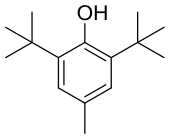
28% bis- and traces of tris-substitution. The desired product was successfully purified from the other regioisomers, however after several attempts it could not be separated from unreacted **131** and was omitted from the final substrate scope.[xix]

Table 33. Attempted *O*-centred nucleophilic substitution of **92a** with different bulky phenols[a]



92a

132-134
2.0 equiv

Entry	Substrate	Product distribution[b]	Entry	Substrate	Product distribution[b]
1	 **132**	96% conversion 2% O-coupling 59% C3-coupling products arising from H_2O	3	 **134**	64% conversion 26% O-coupling no C3-coupling products arising from H_2O
2	 **133**	No O- or C3 coupling only products arising from H_2O			

[a]Reaction Conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **92a** in a 0.17 M solution of MeCN, 5 mol % **55** and 2.0 equiv of nucleophile (**132-134**) at 90 °C for 30 min in a 10 mL sealed vial. [b]Product distribution was determined by ^{1}H NMR analysis using mesitylene or trimethoxybenzene as the internal standard.

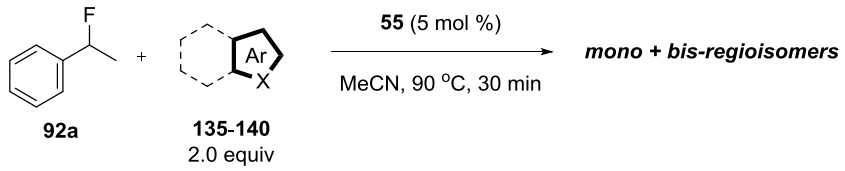
As shown in Table 33, a number of phenols were tolerated with reaction occurring almost exclusively through an electron-rich ring carbon and not through the oxygen atom; this regioselectivity can be advantageous as coupling can occur in the presence of a free hydroxyl which could be later functionalised. However, to investigate the conditions required to promote substitution at oxygen, substrates were tested that had the most reactive *ortho* and *para* positions blocked (**132**-**134**) and the results are shown in Table 33. 2,4,6-trimethylphenol (**132**) only afforded small amounts of reaction through the oxygen (2%), surprisingly 59% substitution at the sterically hindered *meta* position was observed. 2,6-di-*tert*-butyl-4-methylphenol (**133**) was too bulky for reaction to occur at C3 but unfortunately no coupling through oxygen was detected either, with the only products observed originating from reaction with water. Finally coupling through oxygen was observed with the electron-deficient 2,4,6-trifluorophenol (**134**), however the reaction is slow with 64% conversion after 30 mins to 26% phenolic ether and again water derived products. Due to

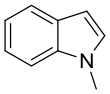
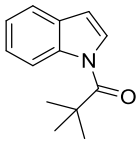
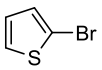
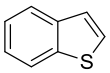
[xix] σ_m: F = 0.34; Cl = 0.37; Br = 0.39; I = 0.35; CF_3 = 0.43. σ_p: F = 0.06; Cl = 0.23; Br = 0.23; I = 0.18; CF_3 = 0.54.[86]

volatility this compound was difficult to dry using standard methods and could not be successfully recrystallised, and thus was not further pursued.

Several heteroarenes were tested (Table 34). *N*-Methylindole (**135**) gave a mixture of regioisomers with the major product detected in 48% yield; unfortunately it could not be successfully purified. The less electron-rich *N*-pivaloyl protected indole (**136**) gave better selectivity with 66% of the major regioisomer but again isolation was unsuccessful. A much cleaner reaction could be achieved with the inclusion of deactivating groups on the 5-position and consequently 5-nitro-3-(1-phenylethyl)-1-pivaloylindole **92s** and 5-cyano-3-(1-phenylethyl)-1-pivaloylindole **92t** were isolated in 51% and 54% yield, respectively (Table 31).

Table 34. Attempted nucleophilic substitution of **92a** with different heteroarenes[a]



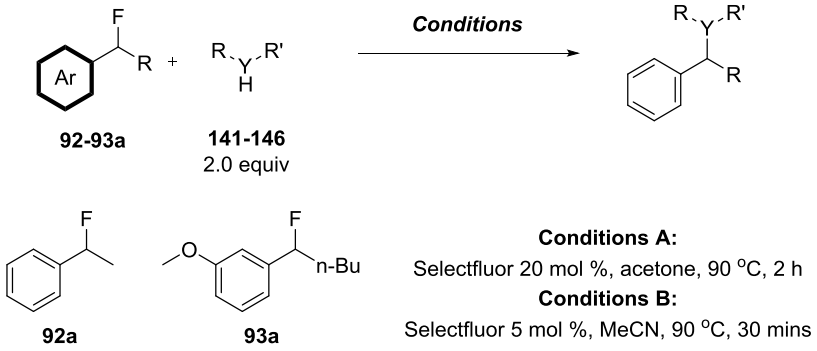
Entry	Substrate	Product distribution[a]	Entry	Substrate	Product distribution[a]
1	 **135**	>99% conversion several inseparable regioisomers, major = 48%	5	 **138**	>99% conversion complex mixture of regioisomers
2	 **136**	>99% conversion several inseparable regioisomers, major = 66%	6	 **139**	92% conversion complex mixture of regioisomers
3	 **137**	>99% conversion several inseparable regioisomers, major = 66%	7	 **140**	No coupling with **55** only products arising from H_2O

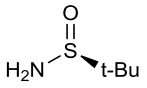
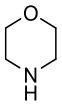
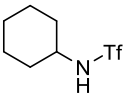
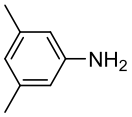
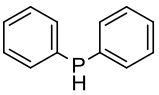
[a]Reaction conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **92a** in a 0.17 M solution of MeCN, 5 mol % **55** and 2.0 equiv of nucleophile at 90 °C for 30 min in a 10 mL sealed vial.[b]Product distribution was determined by ^{1}H NMR analysis using mesitylene or trimethoxybenzene as the internal standard.

Aforementioned, selective C2 or C3 substitution of benzothiophenes could be achieved by blocking the other reactive position with a methyl group (Table 31, **92q** and **92r**), reaction with simple benzothiophene (**137**) gave the major regioisomer in 66%, however it could not be effectively separated from the complex mixture of other mono- and bis-regioisomers (Table 34, entry 3). Thiophenes **138** and **139** were too reactive and a number of mono and bis-regioisomers were observed by NMR and GC-MS. Thiazole (**140**) was completely unreactive. Previously when

nucleophiles are tested that appear to be unreactive in this system, conversion to other by-products arising from reaction of adventitious water is commonly observed. However, in the case of thiazole only 8% conversion occurred. Moreover, the majority of other nitrogen containing nucleophiles tested appeared to completely inhibit reaction of benzylic fluoride substrates **92a** and **93a**. No conversion also occurred in the presence of diphenyl phosphine (**146**) however this may be due to consumption of Selectfluor through oxidation of the phosphine

Table 35. Attempted nucleophilic substitution of **92-93a** with Group XV nucleophiles[a]



Entry	Substrate	Conditions	Product distribution[a]	Entry	Substrate	Conditions	Product distribution[a]
1	 **141**	**A, 93a**	No reaction	5	 **144**	**A, 93a**	No reaction
2	 **142**	**A, 93a**	No reaction	6	 **145**	**B, 92a**	No reaction
3	 **143**	**A, 93a**	No reaction	7	 **146**	**B, 92a**	No reaction

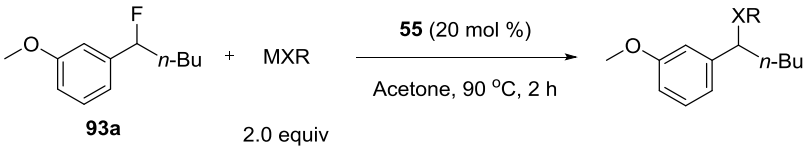
[a]Reaction Conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **92** or **93a** in a 0.17 M solution under conditions A or B in a 10 mL sealed vial. [b]Product distribution was determined by ^{1}H NMR analysis using mesitylene or trimethoxybenzene as the internal standard.

There are two possible explanations for the observed inhibitory role of nitrogenous nucleophiles. Either i) these compounds act as a base quenching any acidic species in the reaction media which may be activating the fluoride or ii) transfer fluorination from Selectfluor occurs resulting in a less electrophilic fluoronium source.[286] If nitrogen nucleophiles are acting as a base in the reaction, to some extent the same argument could be assumed for oxygen nucleophiles. Accordingly, oxygen nucleophiles performed much worse in the reactions catalysed by PTSA (Table 29, entries 10 and 11); however, no drop in reactivity is observed with Selectfluor (Table 29, entries 12-13 and Table

30, entries 4-6). On the other hand, if fluorine transfer from Selectfluor to quinuclidine can occur in less than 10 minutes at room temperature,[286a] it seems likely that under the standard reaction conditions (90 °C) rapid fluorine transfer to the nitrogen nucleophile could occur resulting in a new N-F species which is less electrophilic and therefore unable to activate the C−F bond towards substitution. Aforementioned, a significant decrease in reactivity was observed when other less electrophilic N-F reagents (**51** and **54-OTf**) were employed in the substitution of **117a** with water (Table 28, entries 4 and 5). The only successful C−N coupling occurred with *tert*-butyl tosylcarbamate (Table 31, **92u**); the nitrogen atom in this compound is poorly nucleophilic and may not be able to undergo fluorine transfer at a sufficient rate or if exchange can occur the resulting N-F compound may be reactive enough to facilitate activation of the C−F bond.

Ionic nucleophiles also seem to inhibit reaction (Table 36). Similar to the case of the *N*-nucleophiles, ionic nucleophiles may react with the F^+ resulting in a less electrophilic fluoronium. Selectfluor is extremely oxidising and has been utilised to generate electrophiles from anionic sources ($^-SCN \rightarrow {}^+SCN$)[287] and thus the F^+ activity of SelectFluor may be consumed in a reductive pathway.

Table 36. Attempted substitution of 1-fluoroethylbenzene **92a** with different ionic nucleophiles[a]



Entry	Substrate	Product distribution[a]
1	KSCN	No reaction
2	KSAc	No reaction
3	KOAc	No reaction
4	NaOTf	No reaction
5	LiCl	No reaction

[a]Reaction conditions: all the reactions were carried out in flame-dried glassware under an Ar atmosphere with 1.0 equiv of **93a** in a 0.17 M solution of acetone, 20 mol % **55** and 2.0 equiv of nucleophile at 90 °C for 2 h in a 10 mL sealed vial. [b]Product distribution was determined by ^1H NMR analysis using mesitylene or trimethoxybenzene as the internal standard.

4.3.6. Mechanistic investigation

This section discusses the experiments carried out to elucidate the role of Selectfluor in activating the fluoride towards substitution and the mechanism by which this substitution event occurs. There are several valuable pieces of information on the function of Selectfluor that can be gleaned from experiments carried out throughout this chapter. In Table 28 the role of additives on the substitution of benzylic fluoride **117a** with water was discussed and it can be seen that both Brønsted and Lewis acids can promote reaction. This was further elaborated in Tables 29 and 30 where the substitution of *O*- and *S*-based nucleophiles was investigated with fluorides **92**-**93**a. To this point, the theories that Selectfluor could undergo thermal decomposition to produce HF[xx] or may contain traces of the protonated DABCO[xx]-type conjugate base of Selectfluor were considered and the optimisation was carried out with Selectfluor and PTSA[xx]. Both catalysts gave good to excellent results with thiol **92g** (<73%), however on switching to the alcohols **123** and **124** a marked decrease in reactivity was observed for the PTSA catalysed system (~30% conversion and 13-18% product) but not SelectFluor, which again gave excellent conversion (>99%) and product yield (88 to >99%). Taking this disparity into account it seems unlikely that trace amounts of acid in Selectfluor are responsible for reaction and instead Selectfluor may function as a Lewis acid (a theory which has been suggested previously although there is no concrete proof).[285]

Although the lone-pair electrons on organic fluorine are less available for bonding than oxygen or nitrogen, Paquin and co-workers showed that they can interact with hydrogen-bond donor solvents permitting substitution at the electrophilic carbon. The molecular orbitals of 1-fluoroethylbenzene (**92a**) and Selectfluor II (**56**) were calculated using the Gaussian '09 package (B3LYP/6-31g). The HOMO and HOMO−1 for **92a** showed the π-system of the arene being the contributing orbitals however the non-bonding electrons on the fluoride are clearly visible in the HOMO-2; in addition the LUMO of Selectfluor II shows a large anti-bonding orbital contribution on the electrophilic fluorine (Figure 13). Therefore, it is feasible that the electrophilic fluorine atom could act a Lewis acid and interact with the lone pair electrons on the fluorine atom of **92a**, which seem accessible and not too low in energy. Furthermore, the observation that other commercially available sources of F^+ which are known to be less oxidising/electrophilic performed worse in the nucleophilic substitution with water (Table 28) and that nitrogen containing compounds inhibit reaction (Table 35) through the potential formation of weaker sources of fluoronium adds credence to the theory that Selectfluor is acting as a Lewis acid in this reaction.

[xx] pK_a HF = 3.17 (H_2O), 15 (DMSO); pK_aH DABCO = 2.97, 8.83 (H_2O), 2.97, 8.93 (DMSO); pK_a PTSA = −2.8 (H_2O), 8.5 (MeCN).[288]

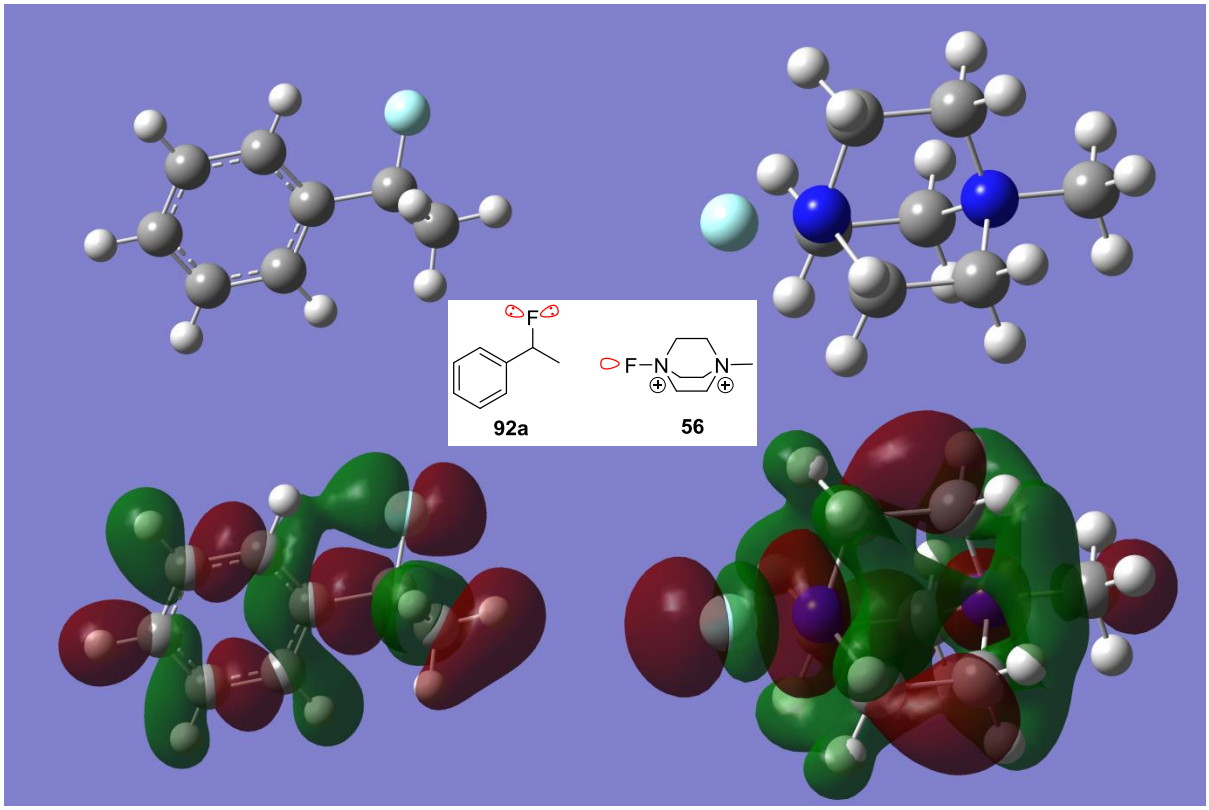
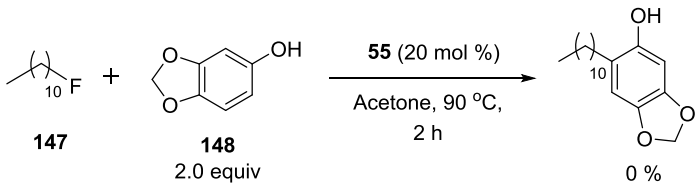


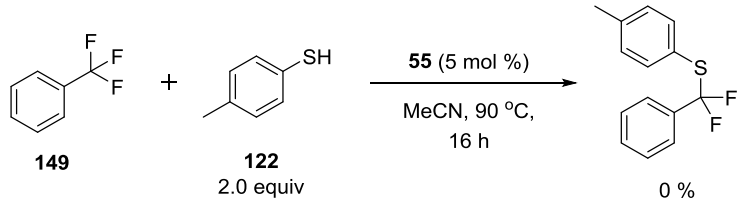
Figure 13. Possible interacting orbitals on a **92a** (HOMO-2) and **55** (LUMO)

The three possible mechanisms by which substitution in this system occurs include: S_N1, S_N2 and E1 elimination then nucleophilic addition. Hilmersson *et al.* reported that the ytterbium mediated iodination of alkyl fluorides occurs via a S_N2 route.[264] Consequently, 1-fluorodecane (**147**) gave no conversion in the presence of 2 equiv of sesamol (**148**) and 20 mol % Selectfluor **55** (Scheme 125). This experiment does not rule out a S_N2 mechanism but simply shows that alkyl fluorides are not suitable substrates.



Scheme 125. Attempted substitution of 1-fluorodecane (**56**).

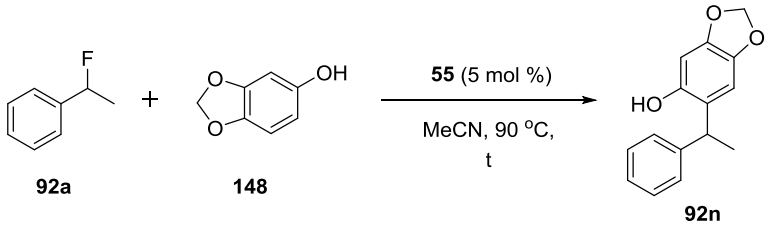
Activation of the benzylic fluorides in a trifluoromethyl group was also not possible with **55** (Scheme 126). Similarly, Hilmersson and co-workers found α,α,α-trifluorotoluene (**149**) resistant to substitution in the presence of YbI_3 at room temperature.



149 **122** 2.0 equiv 0 %

Scheme 126. Attempted substitution of α,α,α-trifluorotoluene (**149**).

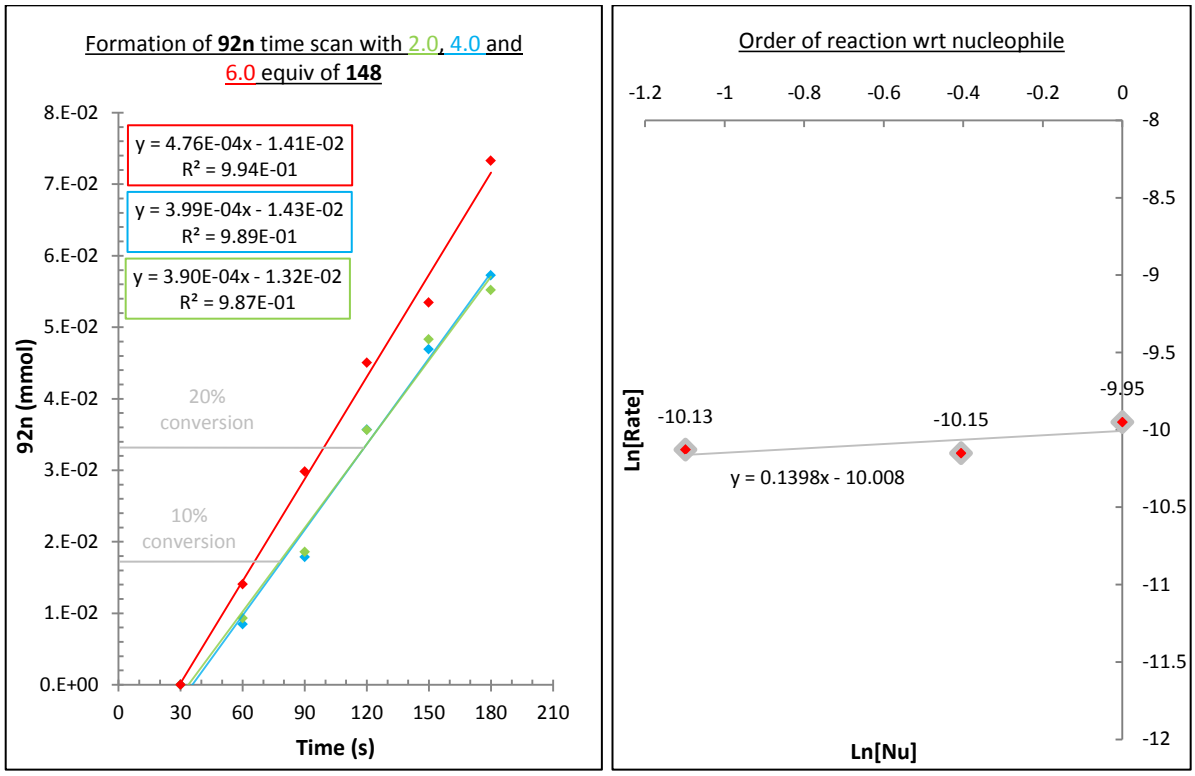
To elucidate whether substitution occurs through a bimolecular transition state, the order of reaction of the nucleophile was determined using the initial rates method and a constant concentration of catalyst (Scheme 127). The initial rate of reaction at three concentrations of **148** was determined.



92a **148** **92n**

Rate = k[**92a**]^m[**148**]^n

if n = 0, ⇒ S_N1 or E1; if n = 1, ⇒ S_N2

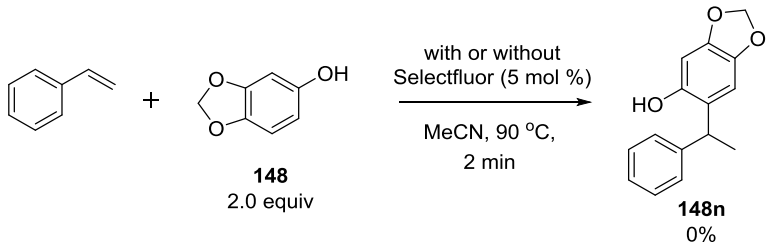


Scheme 127. Determining the order of the nucleophile using the method of initial rates

Unfortunately the reaction of sesamol on fluoride **92a** is so fast that around 20% product (**92n**) is already observed after 2 min. Ideally to calculate the initial rate accurately 10 separate time points would be taken between 0–10% conversion, however this would not be possible with the method used as it would require accurate removal of an aliquot of the reaction mixture and quenching at

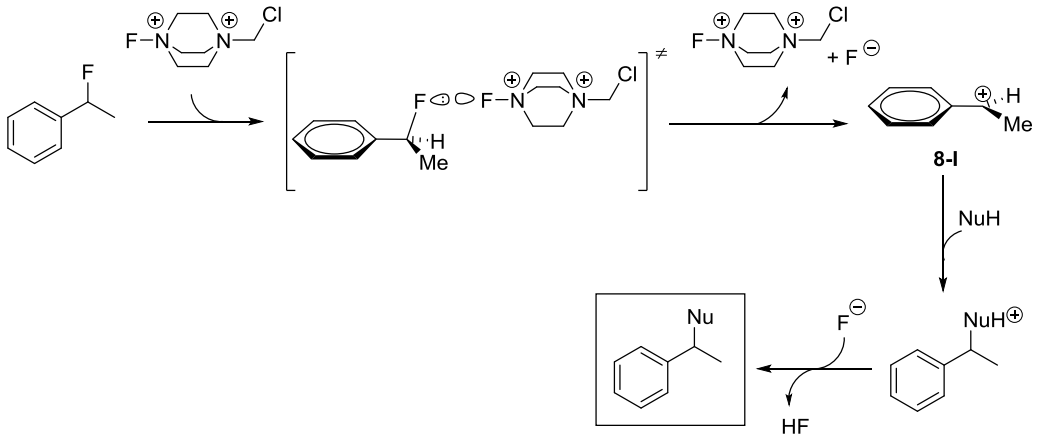
around 7 seconds intervals. When the lines of best fit are considered for the different concentrations, a non-linearity between the origin and the subsequent points can be observed, and is due to the fact that no product was detected at the first time point of 30 seconds. Of course, this does not mean that there was in fact no conversion at this time; instead the concentration may have been too low to be detected by ^{1}H NMR. The rates measured for 2.0 and 4.0 equiv of nucleophile are nearly identical and overlay on the graph, the rate measured at 6.0 equiv of nucleophile is slightly higher but not consistent with 1st order dependence. Moreover, when the natural logs of the rate and nucleophile concentration are plotted it can be clearly seen that the order of the nucleophile is zero (it is difficult to obtain a slope of zero as any change in the y direction has a significant impact on the gradient).

The zero order obtained in relation to the nucleophile rules out an S_N2-type transition state. To investigate the possibility of a mechanism involving E1 elimination the reaction was carried out with styrene (Scheme 128) and no reaction was observed after 2 min. If the reaction proceeded via this intermediate, at least 20% conversion would be expected after this reaction time.



Scheme 128. Attempted substitution of styrene

Based on the evidence so far, it is most likely that the reaction occurs via a uni-molecular rate determining step involving Selectfluor promoted ionisation of the fluoride **92a** to give a carbocation **92-I** which rapidly reacts with a nucleophile resulting in a net loss of HF (Scheme 129).



Scheme 129. Proposed reaction mechanism.

4.3.7. Conclusion and future outlook

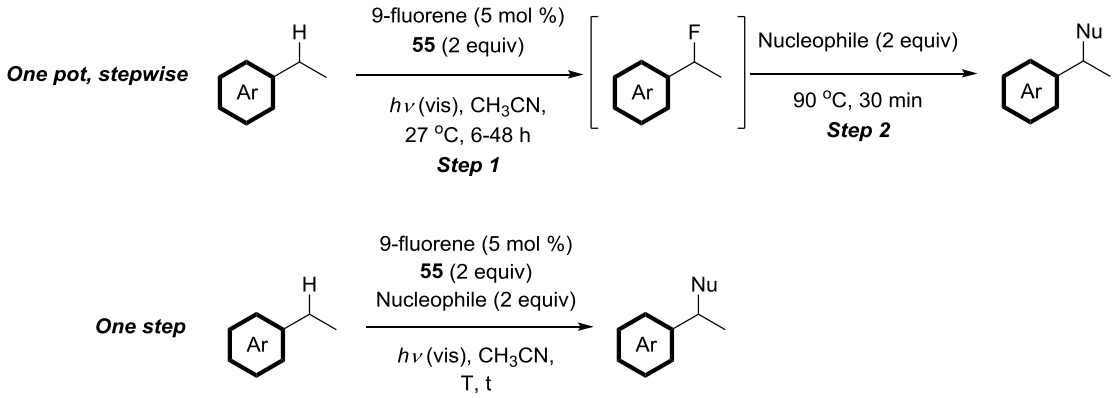
In conclusion, we have expanded upon the initial decarboxylative hydroxylation methodology to extend the scope of the nucleophile showing that a variety of new C–C, C–O, C–S and C–N bonds can be formed, even with poorly nucleophilic species. The decarboxylative hydroxylation reaction occurred via *in situ* formation of a reactive benzylic fluoride intermediate which underwent rapid substitution with water. Due to the reactivity of the fluoride in this system and the requirement for water in the decarboxylation step, the fluoride was isolated to prevent unwanted alcohol formation. The model substrate (1-fluoroethylbenzene **92a**) can be generated in 5 min[xxi] then upon isolation successfully reacted with a number of different nucleophiles in good to excellent yields in 30 minutes or less with 5 mol % of inexpensive Selectfluor. As the conditions are mild and metal-free a variety of synthetically useful substituents are tolerated including halides, alkynes, unprotected alcohols, nitro, nitrile and sulfonamides (Table 31).

Mechanistic studies have elucidated that the most likely course of reaction is through a S_N1 pathway; which involves ionisation of the fluoride to generate a carbo-cation intermediate which rapidly reacts with a nucleophile generating HF and the desired product. Both Brønsted acids and Selectfluor can mediate the reaction in sub-stoichiometric amounts but a differentiation in reactivity is observed when changing from a thiol to a more basic alcohol nucleophile, indicating that the most likely role in which Selectfluor participates is as a Lewis acid through interaction with the σ^*_{N-F} bond and not through latent acidic species formed on decomposition.

Although the methodology is operationally simple and tolerates a variety of substituents in high yields using an inexpensive catalyst, the main drawback is the need to isolate the fluoride. Attempts at a one pot reaction proved unsuccessful as the decarboxylation currently requires water as the co-solvent and the resulting fluoride is too reactive upon activation with Selectfluor and preferentially reacts with water because it is in such a large excess. As discussed in Chapter 3, there are a number of routes that have been recently reported to access benzylic fluorides, however due to the inherent instability[xxii] of these compounds, this moiety should be regarded as building block and not a motif for medicinal chemistry. Thus, a way to improve our methodology and negate the isolation step would be utilise a different route to generate the fluoride. Chen *et al.* reported a photochemical method to access benzylic fluorides using Selectfluor in MeCN.[289,xxi] These conditions are compatible with the nucleophilic substitution, and would tolerate a stepwise approach from ethyl benzenes in which the fluoride is generated, then the nucleophile added, and the reaction mixture heated to 90 ^oC for 30 min with residual amounts of Selectfluor catalysing conversion (Scheme 130). Furthermore,

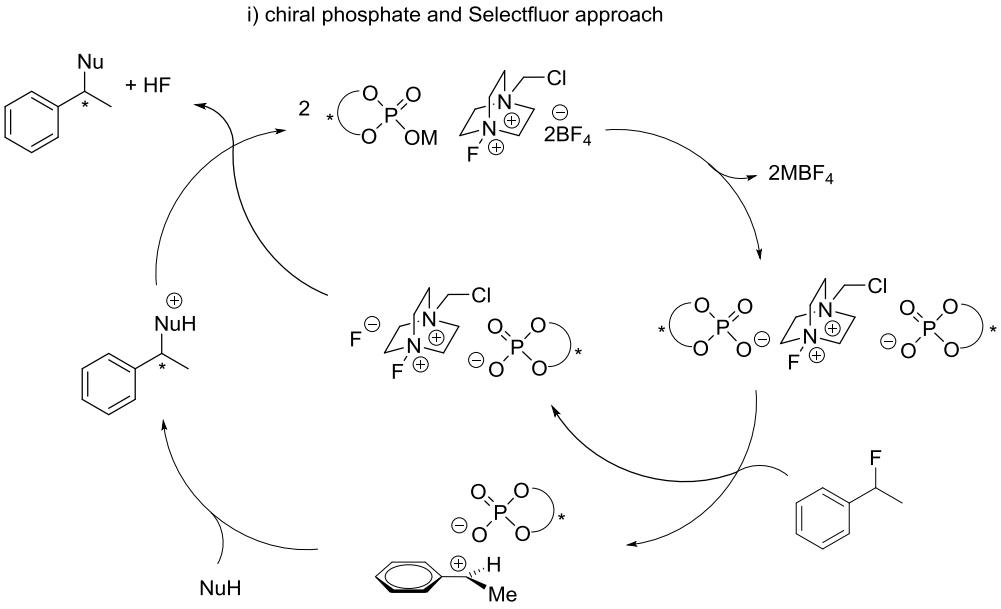
[xxi] Discussed in Chapter 3
[xxii] Which is seldom mentioned by the authors

by optimising reaction temperature and time, it may be possible to carry out the fluorination and substitution consecutively.



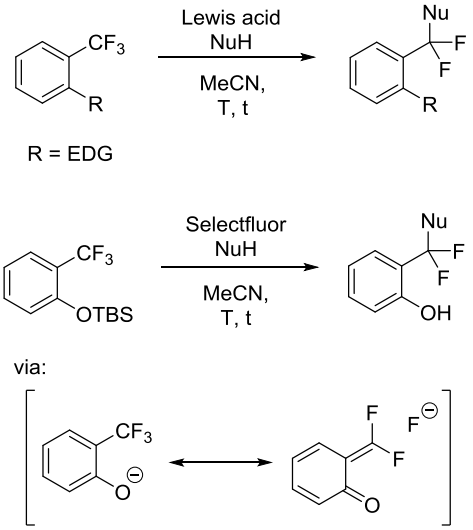
Scheme 130. Modification of reaction negating isolation of the fluoride.

With a view towards a stereoselective reaction, it has been established that the substitution occurs via a S_N1 mechanism and thus stereocontrol would need to be introduced during nucleophilic attack on the carbo-cation as any chirality present in the starting fluoride would be lost during this step. Furthermore, as the substitution can be catalysed by Selectfluor and Brønsted acids it seems plausible that enantio-control could be achieved via chiral ion-pair catalysis[290] using i) chiral anions in conjunction with Selectfluor[291] (Scheme 131) or even ii) chiral acids. However, if this approach is to have any success it would likely require lower temperatures as the thermal energy may be too great to allow successful formation of the ion-pair.[290b,292]



Scheme 131. Possible route to enantioselective substitution via ion-pair catalysis.

Aforementioned, the trifluoromethyl group was resistant to substitution under the optimised reaction conditions, even over prolonged times (Scheme 126). However, as discussed in relation to Scheme 119, Kiselyov amongst others have shown that trifluoromethyl groups can be activated in the presence of base. Thus it seems likely that the trifluoromethyl group to be activated towards nucleophilic substitution allowing access to partially fluorinated compounds. This could be achieved providing a suitable Lewis acid can be identified and/or with the inclusion of an electron-donating group in *ortho* to promote ionisation (Scheme 132). Alternatively, Selectfluor has been utilised under microwave conditions to deprotect TBS phenolic ethers[293]; then *in situ* deprotection of an *ortho* OTBS group could permit substitution of the trifluoromethyl group through negative hyper-conjugation effects (Scheme 132).



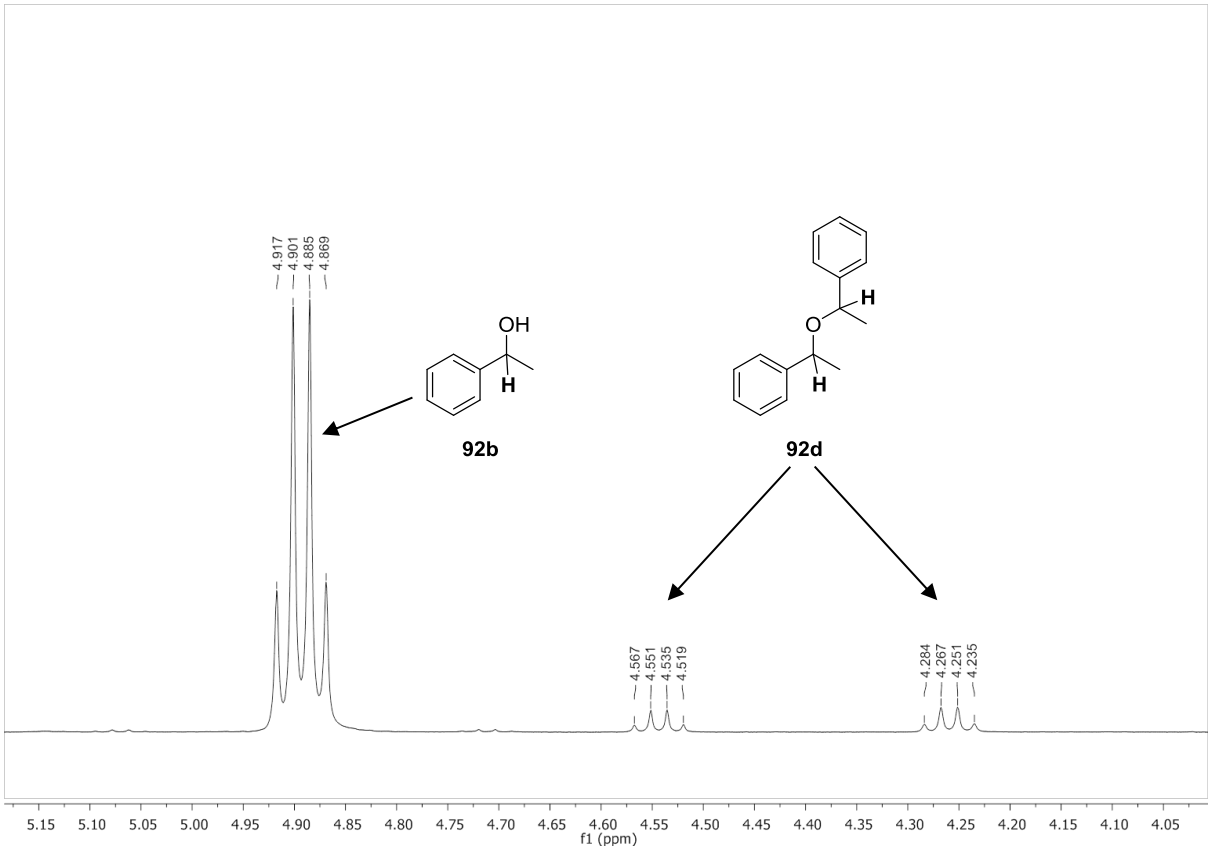
Scheme 132. Possible routes to partially fluorinated compounds via Lewis acid activation of a trifluoromethyl group.

Chapter 4 – Supporting Information

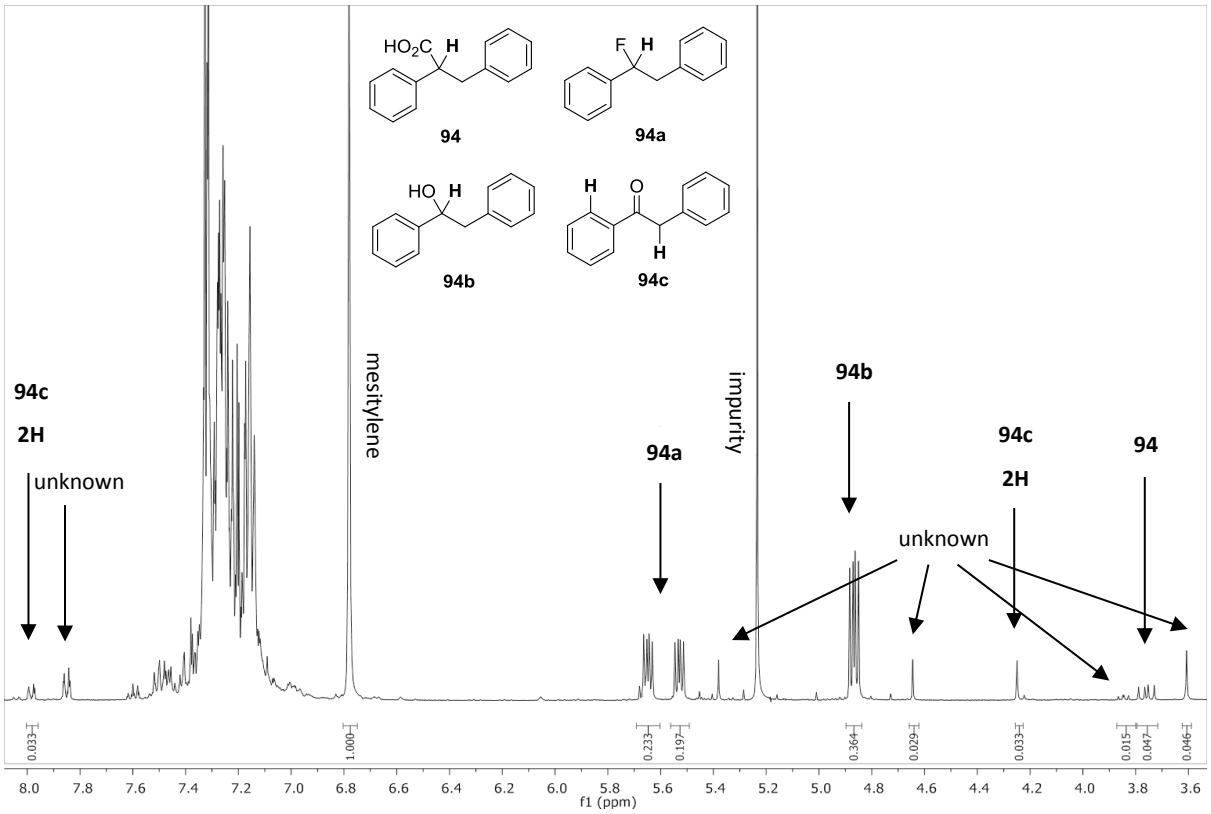
S4.1. OPTIMISATION DATA

S4.1.1. Table 24 – Ether dimer

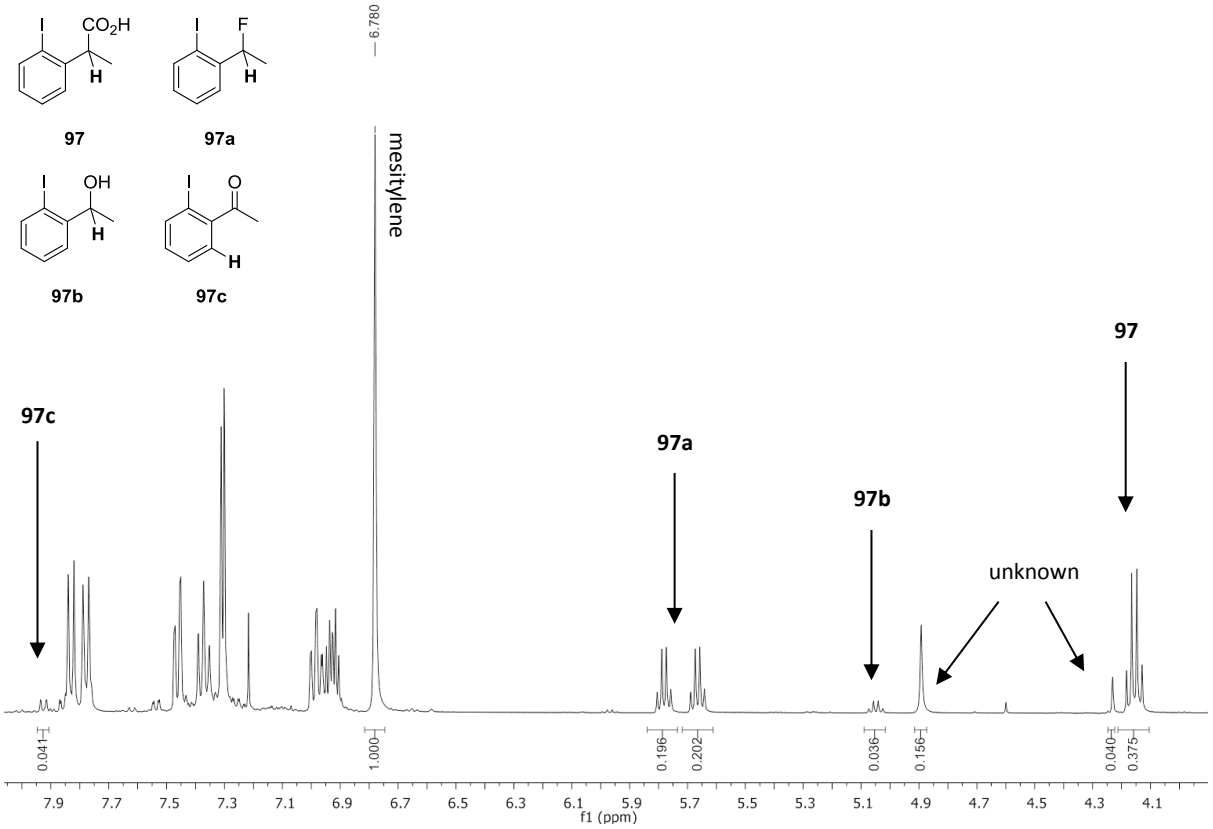
Below is an exemplary spectrum showing a mixture of alcohol **92b** and ether dimer **92d**[294] obtained after **92b** was heated under acidic conditions for 16 h.



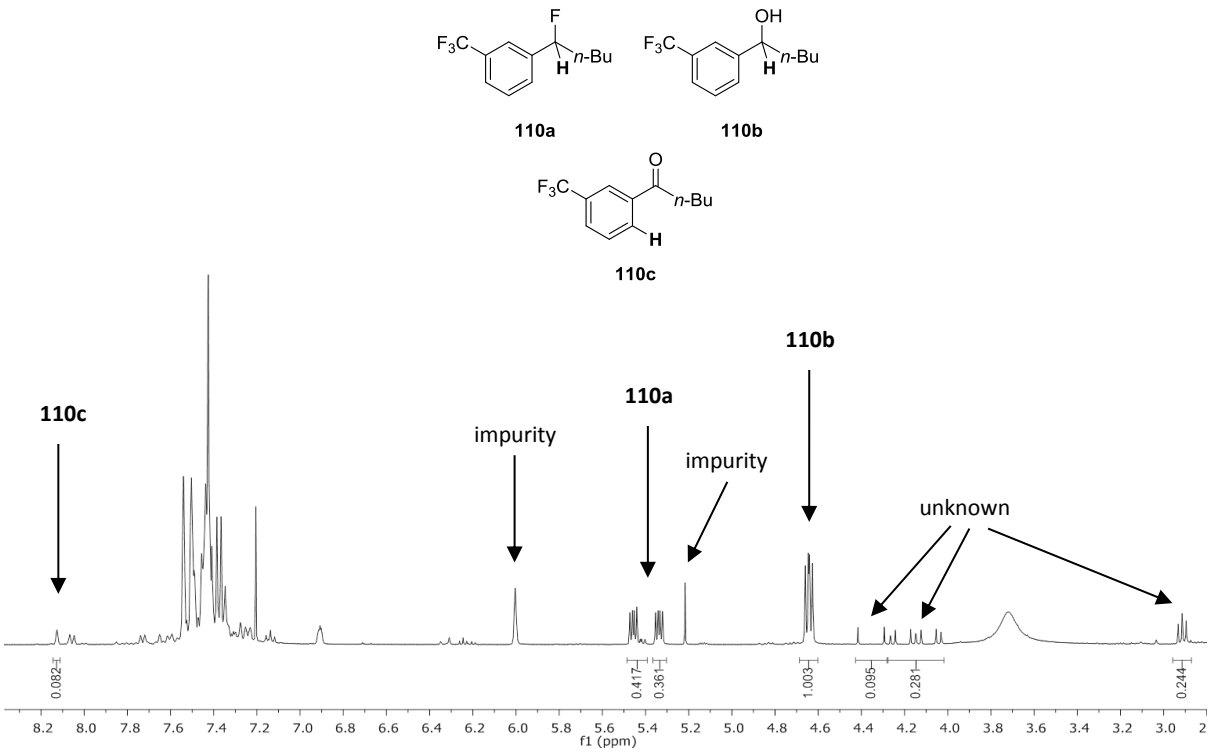
S4.1.2. Table 26 – Entry 1



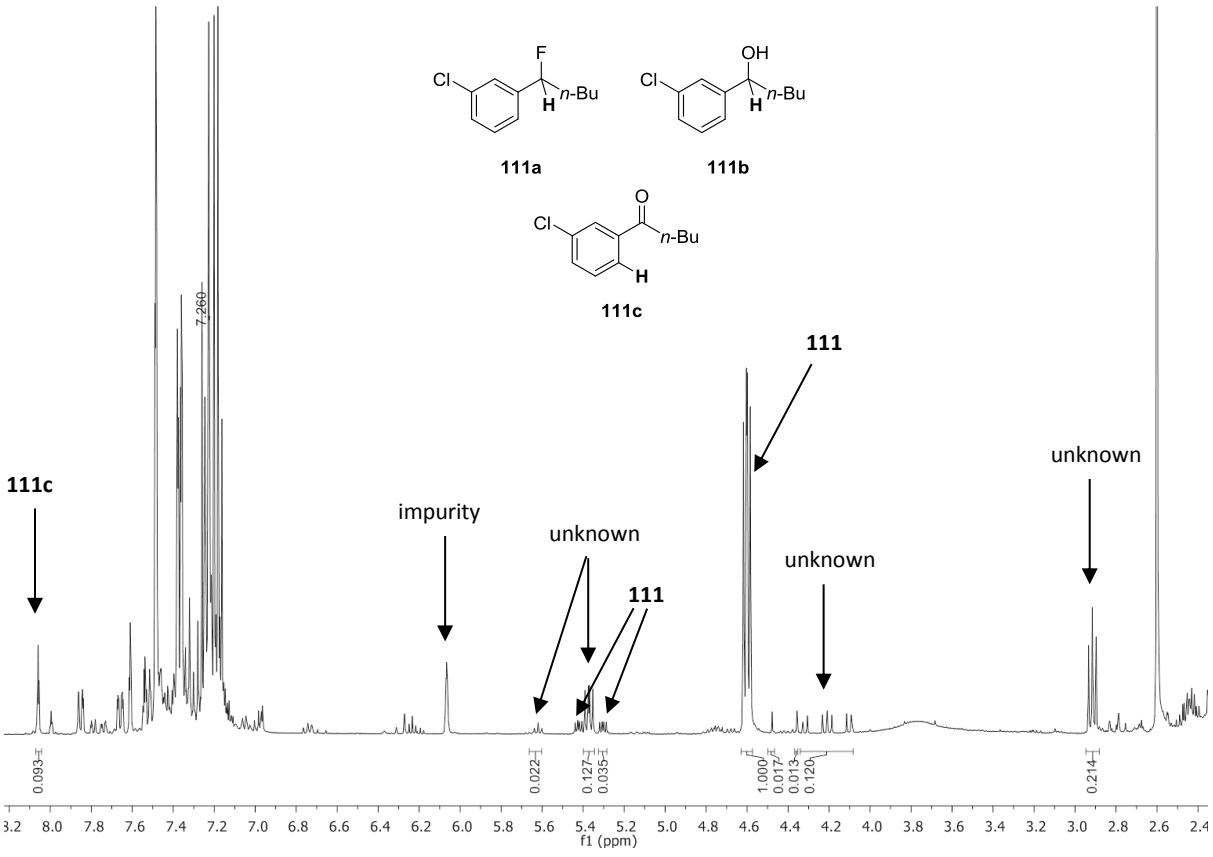
S4.1.3. Table 26 – Entry 3



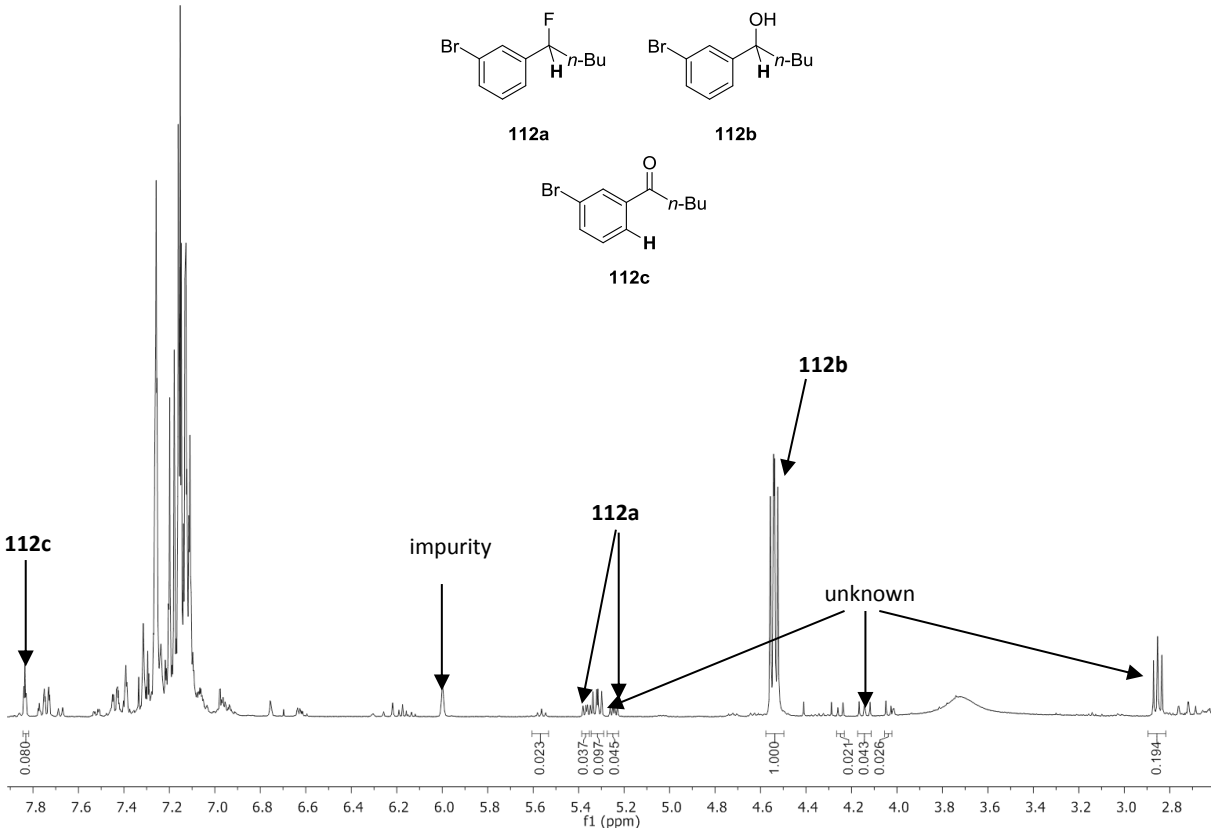
S4.1.3. Table 26 – Entry 6



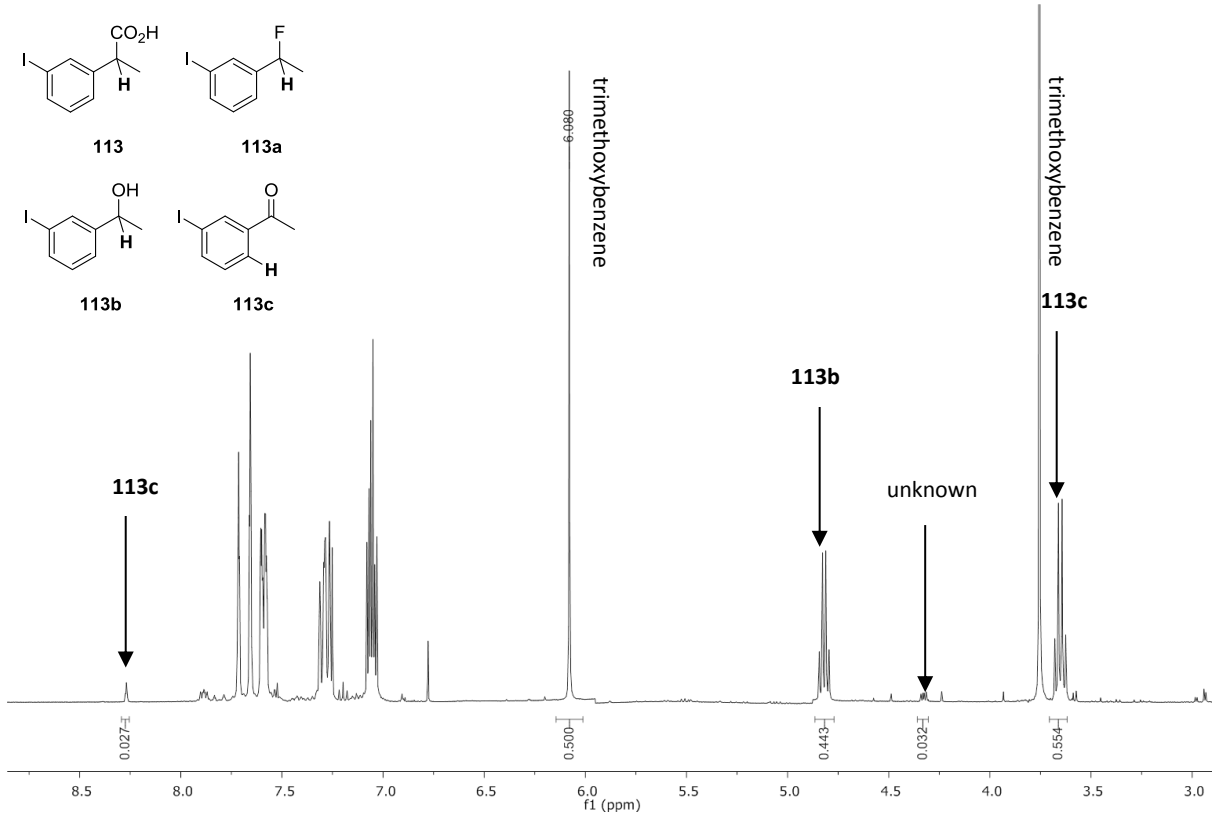
S4.1.4. Table 26 – Entry 7



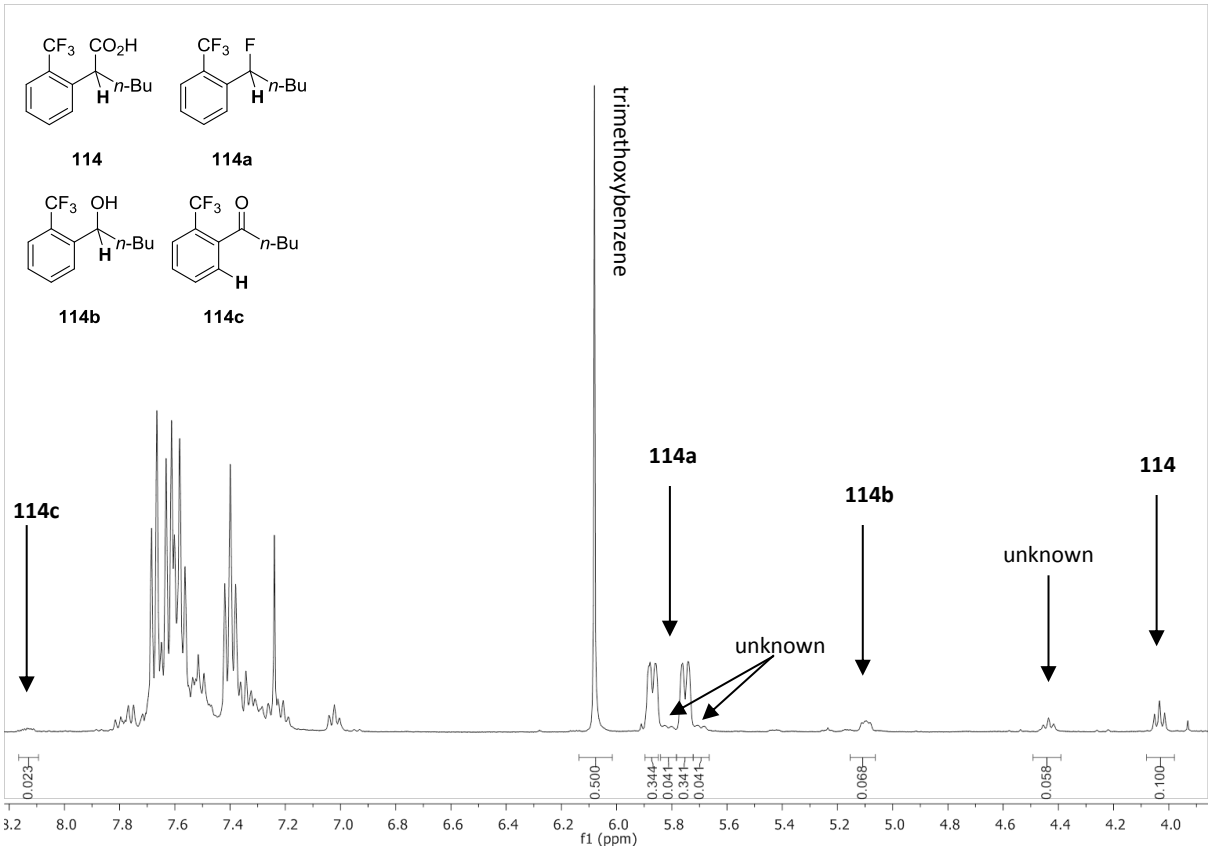
S4.1.4. Table 26 – Entry 8



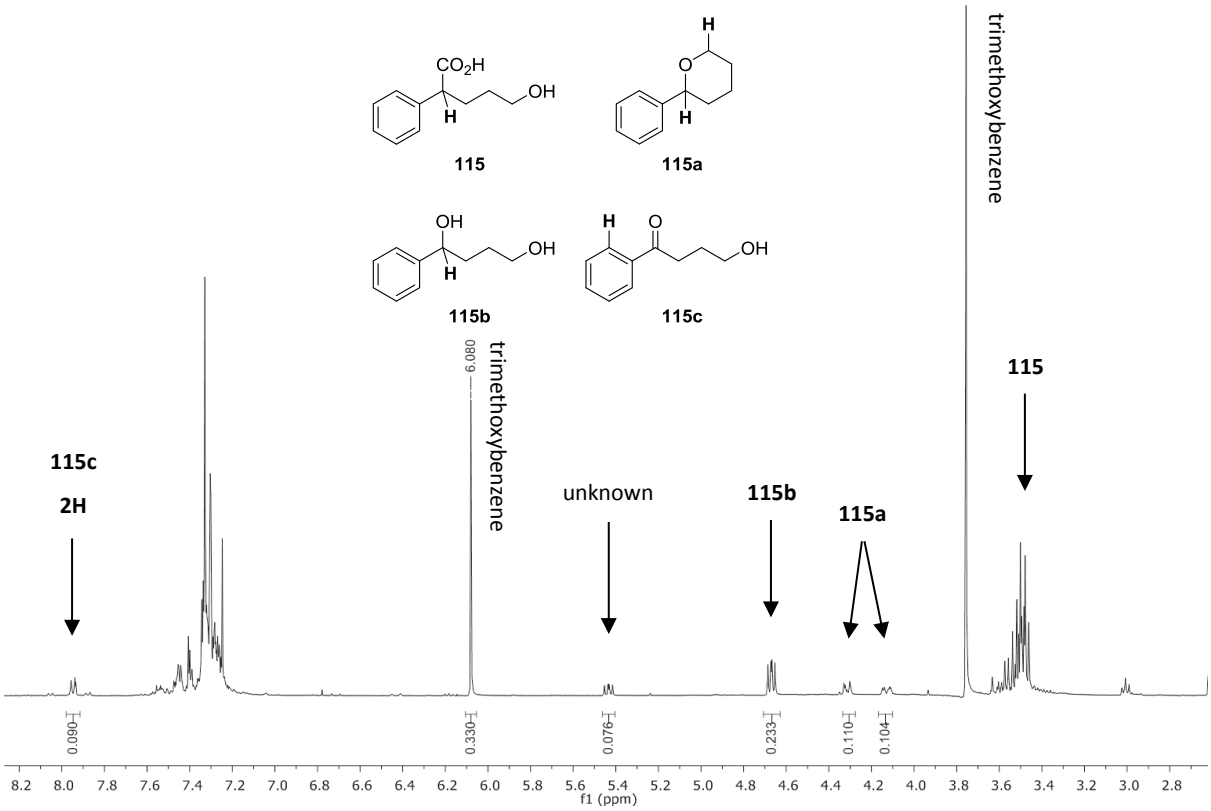
S4.1.5 Table 26 – Entry 9



S4.1.6. Table 26 – Entry 11



S4.1.7. Table 27 – Entry 2[277]

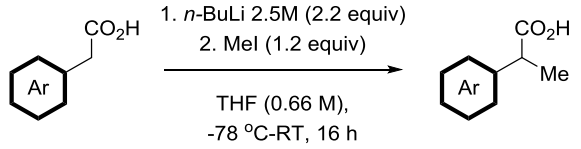


S4.2. GENERAL INFORMATION

Starting material preparation and nucleophilic substitutions were carried out in flame-dried glassware under an Ar atmosphere, all other reactions were carried out without stringent exclusion of moisture. Reagents and anhydrous solvents were obtained from commercial sources and used without further purification, except IPA, TFE and propargyl alcohol which were dried over CaH_2 and distilled prior to use; all phenols were re-crystallised and stored in a desiccator. $AgNO_3$ was purchased from Alfa Aesar (Premion®, 99.9995% (metals basis)), Selectfluor was purchased from Sigma Aldrich (>95%). THF was obtained by Grubbs type solvent purification system. Deionized water was obtained from a Pure Lab Option Elga DV35 purification system. Acids that were not commercially available were synthesised using General Procedures A-D. Column chromatography was carried out using a Biotage Isolera Four purification system using Biotage ZIP® or SNAP® columns. Analytical thin layer chromatography was performed on pre-coated silica gel F254 plates with visualization under UV light and potassium permanganate solution. Melting points were obtained using a Bibby Stuart Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 37 FTIR machine using the thin film methodand are quoted in cm^{-1}. High resolution mass spectra were performed at the EPSRC National Mass Spectrometry Service Centre, Swansea. NMR spectra were recorded on a Bruker AV400 or AVIII400 sprectrometer. ^{1}H NMR spectra, recorded at 400 MHz, are referenced to the residual solvent peak at 7.26 ppm ($CHCl_3$) and quoted in ppm to 2 decimal places with coupling constants (*J*) to the nearest 0.1 Hz, splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), AB quartet (ABq), quintet (quin), septet (sept), multiplet (m). ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the solvent peak at 77.16 ppm ($CDCl_3$) and quoted in ppm to 1 decimal place with coupling constants (*J*) to the nearest 0.1 Hz. ^{19}F NMR spectra were recorded at 376 MHz.

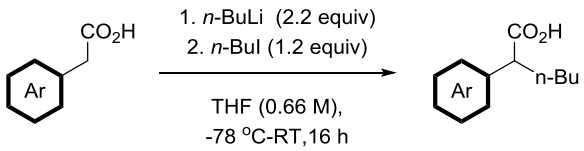
S4.3. GENERAL PROCEDURES

General Procedure A



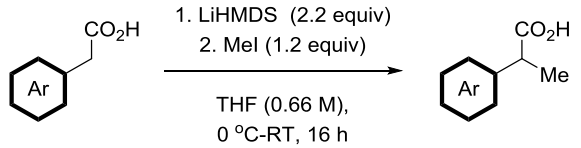
n-BuLi (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at -78 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. MeI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **109.**

General Procedure B



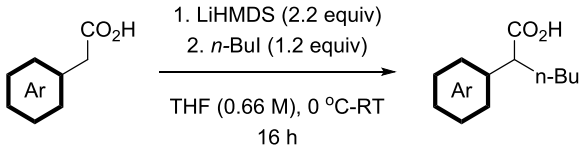
n-BuLi (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at -78 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. *n*-BuI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **110** & **114**.

General Procedure C



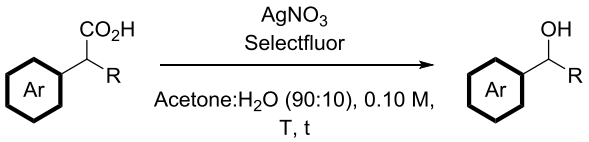
LiHMDS (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66 M) at 0 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. MeI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by column chromatography or recrystallisation in the specified eluents to afford products **113.**

General Procedure D



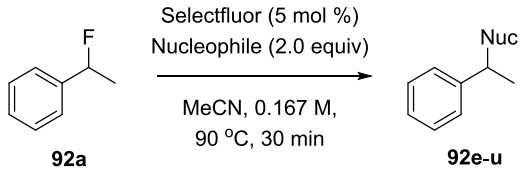
LiHMDS (2.2 equiv) was added dropwise to a solution of a phenylacetic acid in THF (0.66M) at 0 °C, and the reaction mixture was stirred vigorously at this temperature for 1 h. *n*-BuI (1.2 equiv) was then added dropwise, the cooling bath removed and the reaction mixture stirred at room temperature for 16 h. .After this time, the reaction was quenched with H_2O and the THF removed *in vacuo*. The resulting residue was dissolved in Et_2O and acidified with 1 M HCl, the organic layer was separated and the aqueous layer extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by automated column chromatography in the specified eluents to afford products **111** & **112.**

General Procedure E



The stated amount of Selectfluor and a phenylpropanoic acid (1 mmol) were weighed into a 20 mL crimp cap vial and dissolved in a 90:10 solution of acetone:H_2O (8.33 mL). The stated amount of $AgNO_3$ was added and the reaction vessel quickly sealed, covered in foil and stirred at the stated temperature for the stated amount of time. After this time, the reaction mixture was rapidly cooled in an ice bath and quenched with 1 M HCl (1 mL). The reaction mixture was diluted in DCM (10 mL) and saturated K_2CO_3 solution was added (2 mL). The organic layer was separated and the aqueous layer with DCM (2 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Products **92-96b**, **98-99b**, **107-113b** were purified by column chromatography in the specified eluents.

General Procedure F



*To carry out the nucleophilic substitution reactions, a large batch (5–10 mmol) of (1-fluoroethyl)benzene **92a** was prepared and used as a solution in anhydrous MeCN. Prior to reaction the concentration of the solution was calculated using ^1H NMR and trimethoxybenzene as the internal standard. The required amount of (1-fluoroethyl)benzene solution was then syringed into a crimp cap vial with the other reagents and the overall concentration adjusted to 0.167 M with additional anhydrous MeCN.*

Selectfluor (0.05 equiv) and the stated nucleophile (2.0 equiv) were weighed into an oven dried 10 mL crimp cap vial and purged with argon. A solution of (1-fluoroethyl)benzene **92a** (1.0 equiv) in MeCN was added, the overall concentration was adjusted to 0.167 M with additional MeCN. The vial sealed and heated to 90 °C for 30 min (for volatile compounds the Ar purge was performed on the

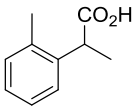
vial containing Selectfluor before addition of the nucleophile). After 30 min the reaction vessel was cooled in an ice bath then diluted with Et_2O, the crude reaction mixture was filtered through a short plug of silica washing with Et_2O (3 × 5 mL) and concentrated *in vacuo*. The yield was determined by ^1H NMR using mesitylene or trimethoxybenzene as an internal standard. Products **92e-92u** were purified by column chromatography in the specified eluents.

S4.4. CHARACTERISATION DATA

S4.4.1. Starting materials

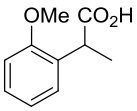
2-Phenylpropionic acid **92**, 2-(3-benzoylphenyl)propanoic acid **95** (Ketoprofen), 2-fluoro-α-methyl-4-biphenylacetic acid (Flurbiprofen) **96** and 4-isobutyl-α-methylphenylacetic acid **107** (Ibuprofen), are commercially available. For the synthesis of compounds **93-94**, **97-99** see Chapter 3.

2-(*o*-Tolyl)propanoic acid 108[234]



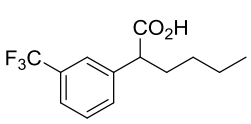
General procedure A was applied with 2-(*o*-tolyl)acetic acid (1.5 g, 10 mmol), *n*-BuLi 2.5 M (8.8 mL, 22 mmol) and MeI (1.17 mL, 12 mmol) in THF (15 mL). The crude was recrystallised twice with *i*-Pr_2O to afford **108** as off white solid (0.52 g, 32%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 6.8 Hz, 1H), 7.23 – 7.14 (m, 3H), 3.99 (q, *J* = 7.1 Hz, 1H), 2.38 (s, 3H), 1.50 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 138.3, 135.9, 130.6, 127.2, 126.6, 126.5, 41.0, 19.6, 17.5.

2-(2-Methoxyphenyl)propanoic acid 109[234]



General procedure A was applied with 2-(2-methoxyphenyl)acetic acid (1.7 g, 10 mmol), LiHMDS 1.0M (11 mL, 11 mmol) and MeI (0.69 mL, 12 mmol) in THF (15 mL). The crude was recrystallised with *i*-Pr_2O to afford **109** as a white crystalline solid (0.81 g, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H, COOH,) 7.29 – 7.22 (m, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 1.49 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8, 156.9, 128.9, 128.5, 128.2, 121.0, 110.9, 55.6, 39.2, 17.0.

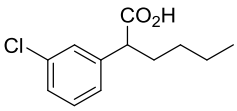
2-(3-(Trifluoromethyl)phenyl)hexanoic acid 110



General procedure B was applied with 2-(3-(trifluoromethyl)phenyl)acetic acid (2.1 g, 10 mmol), *n*-BuLi 2.5 M (8.8 mL, 22 mmol) and *n*-BuI (1.38 mL, 12 mmol) in THF (15 mL). The crude was purified by a short plug of silica eluting 50:50 hexane:Et_2O to afford **110** as a viscous yellow oil (2.45 g, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H, COOH), 7.59 (s, 1H), 7.54 (t, *J* = 6.8 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 3.62 (t, *J* = 7.7 Hz,

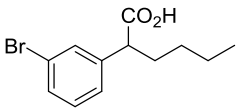
1H), 2.20 – 2.05 (m, 1H), 1.88 – 1.73 (m, 1H), 1.44 – 1.14 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 139.6 , 131.6 (d, *J* = 1.41 Hz, 1C), 131.2 (q, *J* = 32.6 Hz, 1C), 129.3, 125.1 (q, *J* = 3.7 Hz, 1C), 124.5 (q, *J* = 3.7 Hz, 1C), 124.2 (q *J* = 272.2 Hz, 1C), 51.6, 33.0, 30.0, 22.5, 13.9. ^{19}F{^{1}H] NMR (376 MHz, $CDCl_3$) δ -62.6. IR: *v*max (cm^{-1}) = 3000 (O−H), 2960 (C−H), 1706 (C=O), 1327 (C−O), 1164 (CF_3), 1123 (CF_3), 701 (C−H 1,3-disub benzene). HRMS +*p* APCI *m/z* calcd. $C_{13}H_{15}F_3O_2$: $[M+H]^+$ = 261.1097; found = 261.1093.

2-(3-Chlorophenyl)hexanoic acid 111[295]



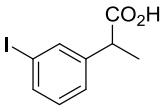
General procedure D was applied with 2-(3-chlorophenyl)acetic acid (1.3 g, 5 mmol), LiHMDS 1.0M (11 mL, 11 mmol) and *n*-BuI (0.69 mL, 6 mmol) in THF (7.5 mL). The crude was purified by automated column chromatography eluting a gradient of 88:12 hexane:Et_2O to 100% Et_2O to afford **111** as a pale yellow oil (0.43 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H, COOH), 7.33 (s, 1H), 7.28 – 7.17 (m, 3H), 3.52 (t, *J* = 7.7 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.73 – 1.82 (m, 1H), 1.40 – 1.19 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 140.4, 134.5, 129.8, 128.2, 127.7, 126.3, 51.3, 32.7, 29.5, 22.3, 13.8.

2-(3-Bromophenyl)hexanoic acid 112[296]



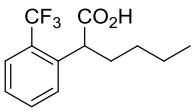
General procedure D was applied with 2-(3-bromophenyl)acetic acid (1.4 g, 5 mmol), LiHMDS 1.0M (11mL, 11 mmol) and *n*-BuI (0.69 mL, 6 mmol) in THF (7.5 mL). The crude was purified by automated column chromatography eluting a gradient of 88:12 hexane:Et_2O to 100% Et_2O to afford **112** as an colourless oil (0.90 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (br s, 1H, COOH), 7.48 (t, *J* = 1.7 Hz, 1H), 7.41 (ddd, 1H, *J* = 7.8, 6.3, 0.6 Hz, 1H), 7.25 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 3.50 (t, *J* = 7.7 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.77 (m, 1H), 1.40 – 1.19 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 140.9, 131.3, 130.7, 130.3, 126.9, 122.8, 51.4, 32.9, 29.7, 22.5, 13.9.

2-(3-Iodophenyl)propanoic acid 113[232]



General procedure C was applied with 2-(3-iodophenyl)acetic acid (1.1 g, 4 mmol), LiHMDS 1.0 M (8.8 mL, 8.8 mmol) and MeI (0.30 mL, 4.8 mmol) in THF (6 mL). The crude was purified by automated column chromatography eluting a gradient of 88:12 hexane:Et_2O to 100% Et_2O to afford **113** as an pale yellow amorphous solid (0.72 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (t, *J* = 1.7 Hz, 1H), 7.61 (ddd, *J* = 7.9, 1.7, 1.1 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 3.67 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 143.2, 138.5, 136.1, 131.8, 129.4, 97.4, 46.8, 17.4.

2-(2-(Trifluoromethyl)phenyl)hexanoic acid 114

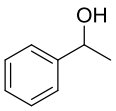


General procedure B was applied with 2-(2-(trifluoromethyl)phenyl)acetic acid (1.0 g, 5 mmol), *n*-BuLi 2.5 M (4.4 mL, 11 mmol) and *n*-BuI (0.69 mL, 6 mmol) in THF (7.5 mL). The crude was purified by automated column chromatography eluting 95:5 hexane:EtOAc to 60:40 hexane:EtOAc afford **114** as a pale yellow solid (0.80 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.04 (t, *J* = 7.4 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.84 – 1.72 (m, 1H), 1.40 – 1.27 (m, 3H), 1.24 – 1.16 (M, 1H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 137.5 (app d, *J* = 1.5 Hz), 132.1, 129.0, 128.9 (q, *J* = 29.2 Hz, 1C), 127.2, 125.91 (q, *J* = 5.8 Hz), 124.2 (q, *J* = 274.2 Hz), 46.3 (app d, *J* = 1.7 Hz), 33.9, 29.7, 22.4, 13.8. ^{19}F{^{1}H] NMR (376 MHz, $CDCl_3$) δ -58.4. IR: *ν*max (cm^{-1}) = 3000 (O−H), 2964 (C−H), 1701 (C=O), 1313 (C−O), 1162 (CF_3), 1118 (CF_3), 769 (C−H 1,2-disub benzene). HRMS −*p* NSI *m/z* calcd. $C_{13}H_{15}F_3O_2$: $[M-H]^-$ = 259.0951; found = 259.0946.

S4.4.2. Benzylic alcohols

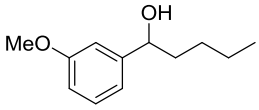
All reactions were carried out in accordance with general procedure E at 0.12 M concentration; the reaction scale, amounts of $AgNO_3$ and Selectfluor, the temperature and time for each reaction are specified below.

1-Phenylethan-1-ol 92[297]



General procedure E was applied with **92** (141 µL, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 3 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 93:7 hexane:Et_2O to 40:60 hexane:Et_2O to afford **92b** as a colourless oil (61 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 4H), 7.31 – 7.25 (m, 1H), 4.90 (q, *J* = 6.4 Hz, 1H), 1.85 (s, 1H), 1.51 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 128.5, 127.5, 125.6, 70.4, 25.1.

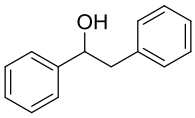
1-(3-Methoxyphenyl)pentan-1-ol 93b[298]



General procedure E was applied with **93** (222 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 3 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:$Et_2O$to 60:40 hexane:Et_2O to afford **93b** as a pale yellow oil (132 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 3.1 Hz, 1H), 6.90 (s, 1H), 6.80 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 4.61 (t, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 2.12 (s, 1H), 1.84 –

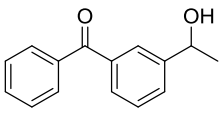
1.61 (m, 2H), 1.45 – 1.21 (m, 4H), 0.95 – 0.82 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 146.9, 129.5, 118.4, 113.0 , 111.5, 74.7, 55.3, 38.9, 28.1, 22.7, 14.1.

1,2-Diphenylethan-1-ol 94b[299]



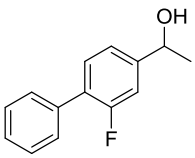
General procedure E was applied with **94** (124 mg, 0.55 mmol), Selectfluor (256 mg, 0.688 mmol), $AgNO_3$ (18.7 mg, 0.11 mmol) in acetone:H_2O (4.14 mL : 450 µL), heated to 90 °C for 6 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **94b** as a white crystalline solid (44 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 12H), 4.91 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.03 (m, 2H), 1.92 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 138.2, 129.7 (2C), 128.7 (2C), 128.6 (2C), 127.8, 126.8, 126.1 (2C), 75.5, 46.3.

(3-(1-Hydroxyethyl)phenyl)(phenyl)methanone 95b



General procedure E was applied with **95** (254 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 6 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **95b** as a viscous yellow oil, (153 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 3H), 7.68 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.66 – 7.54 (m, 2H), 7.47 (dd, *J* = 16.2, 7.9 Hz, 3H), 4.98 (d, *J* = 6.5 Hz, 1H), 1.95 (s, 1H), 1.53 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 146.3, 138.0, 137.7, 132.6, 130.2 (2C), 129.6, 129.4, 128.6, 128.5 (2C), 127.1, 70.2, 25.5. IR: *v*max (cm^{-1}) = 3403 (O−H), 2971 (C−H), 1653 (C=O), 1596 (C−C), 719 (*m*-disub benzene), 699 (monosub benzene). HRMS +p APCI *m/z* calcd. $C_{15}H_{14}O_2$: $[M+H]^+$ = 227.1067; found = 227.1066.

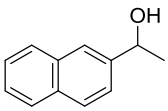
1-(2-Fluoro-[1,1'-biphenyl]-4-yl)ethan-1-ol 96b



General procedure E was applied with **96** (247 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 5 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc to afford **96b** as a slowly crystallising off white solid (106 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.48 – 7.35 (m, 4H), 7.22 (t, *J* = 1.7 Hz, 1H), 7.20 (dd, *J* = 5.7, 1.5 Hz, 1H), 4.94 (q, *J* = 6.4 Hz, 1H), 1.92 (s, 1H), 1.54 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (d, *J* = 248.7 Hz), 147.6 (d, *J* = 6.8 Hz), 135.7, 130.9 (d, *J* = 4.0 Hz), 129.1 (2C), 128.6 (2C), 128.1 (d, *J* = 13.8 Hz), 127.8, 121.4 (d, *J* = 3.4 Hz), 113.2 (d, *J* = 23.5 Hz), 69.73 (d, *J* = 1.0 Hz), 25.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.6. IR: *v*max (cm^{-1}) =

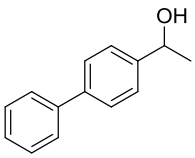
3317 (O−H), 1483 (C=C aryl), 1416 (C=C aryl), 1070 (C−F), 867 (C−H 1,2,4-trisub benzene), 696 (monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{14}H_{13}FO$: $[M]^+$ = 216.0945; found = 216.0939.

1-(Naphthalen-2-yl)ethan-1-ol 98b[300]



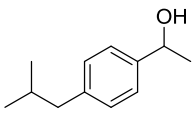
General procedure E was applied with **98** (200 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 3 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **98b** as an off-white amorphous solid (98 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 4H), 7.55 – 7.43 (m, 3H), 5.08 (qd, *J* = 6.1, 2.1 Hz, 1H), 1.87 (d, *J* = 2.9 Hz, 1H, OH), 1.59 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 133.5, 133.1 128.5, 128.1, 127.8, 126.3, 126.0, 124.0 (2C), 70.7, 25.3.

1-([1,1'-Biphenyl]-4-yl)ethan-1-ol 99b[300]



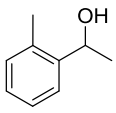
General procedure E was applied with **99** (226 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 1 h in a 10mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **99b** as a white crystalline solid (120 mg, 60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 4H), 7.45 (m, 4H), 7.35 (t, *J* = 7.3 Hz, 1H), 4.96 (q, *J* = 6.4 Hz, 1H), 1.88 (br s, 1H, OH), 1.55 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 141.0, 140.6, 128.9 (2C), 127.4 (3C), 127.2 (2C), 126.0 (2C), 70.3, 25.3.

1-(4-Isobutylphenyl)ethan-1-ol 107b[301]



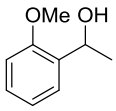
General procedure E was applied with **107** (208 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 80 °C for 5 h in a 10mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **107b** as a colourless oil (131 mg, 74%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.5 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 4.87 (q, *J* = 6.3 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.87 (td, *J* = 13.3, 6.5 Hz, 2H), 1.49 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 141.1, 129.4 (2C), 125.3 (2C), 70.4, 45.2, 30.4, 25.1, 22.5.

1-(*o*-Tolyl)ethan-1-ol 108b[302]



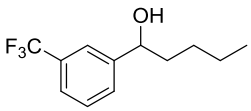
General procedure E was applied with **108** (164 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 80 °C for 3 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:Et_2O to 60:40 hexane:Et_2O to afford **108b** as a pale yellow oil, (73 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.25 (dd, *J* = 11.3, 3.9 Hz, 1H), 7.17 (ddd, *J* = 13.0, 9.5, 4.2 Hz, 2H), 5.14 (q, *J* = 6.4 Hz, 1H), 2.35 (s, 3H), 1.75 (s, 1H), 1.48 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 134.4, 130.5, 127.3, 126.5, 124.6, 67.0, 24.1, 19.1.

1-(2-Methoxyphenyl)ethan-1-ol 109b[300]



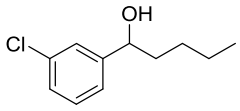
General procedure E was applied with **109** (180 mg, 1.0 mmol), Selectfluor (429 mg, 1.15 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 70 °C for 2 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 95:5 hexane:EtOAc to 60:40 hexane:EtOAc to afford **109b** as a colourless oil (126 mg, 76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.10 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 2.67 (s, 1H), 1.51 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 133.6, 128.4, 126.2, 120.9, 110.6, 66.7, 55.4, 23.0.

1-(3-(Trifluoromethyl)phenyl)pentan-1-ol 110b



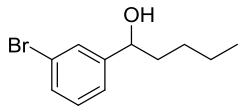
General procedure E was applied with **110** (227 mg, 1.0 mmol), Selectfluor (466 mg, 1.25 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 5 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc to afford **110b** as a yellow oil, (58 mg, 25%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.49 – 7.43 (m, 1H), 4.76 – 4.71 (m, 1H), 1.97 (d, *J* = 3.2 Hz, 1H), 1.85 – 1.66 (m, 2H), 1.47 – 1.22 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 130.9 (q, *J* = 32.2 Hz), 130.4, 129.4, 129.0, 124.4 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272 Hz), 122.8 (q, *J* = 3.7 Hz), 74.2, 39.1, 27.9, 22.7, 14.1. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) -62.6. IR: *v*max (cm^{-1}) = 3352 (O−H), 2934 (C−H), 1162 (CF_3), 1121 (CF_3), 702 (C−H *m*-disub benzene). HRMS +*p* APCI *m/z* calcd. $C_{12}H_{14}F_3O$: $[M-H]^+$ = 231.0991; found = 231.0988.

1-(3-Chlorophenyl)pentan-1-ol 111b[303]



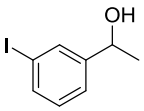
General procedure E was applied with **111** (227 mg, 1.0 mmol), Selectfluor (466 mg, 1.25 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 16 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc to afford **111b** as a pale yellow oil (107 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 1.7 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.24 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 4.61 (t, *J* = 6.6 Hz, 1H), 2.08 (s, 1H), 1.81 – 1.61 (m, 2H), 1.44 – 1.18 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H).

1-(3-Bromophenyl)pentan-1-ol 112b[304]



General procedure E was applied with **112** (270 mg, 1.0 mmol), Selectfluor (466 mg, 1.25 mmol), $AgNO_3$ (34.0 mg, 0.20 mmol) in acetone:H_2O (7.5 mL : 830 µL), heated to 90 °C for 16 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc to afford **112b** as a pale yellow oil, (88 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 1.7 Hz, 1H), 7.25 – 7.15 (m, 3H), 4.60 (dd, *J* = 7.3, 5.9 Hz, 1H), 2.00 (d, *J* = 7.3 Hz, 1H), 1.80 – 1.58 (m, 2H), 1.42 – 1.16 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 134.3, 129.7, 127.6, 126.1, 124.1, 77.4, 77.1, 76.7, 74.1, 38.9, 27.8, 22.6, 14.0.

1-(3-Iodophenyl)ethan-1-ol 113b[14]

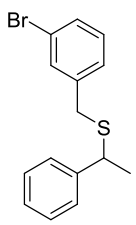


General procedure E was applied with **113** (276 mg, 1.0 mmol), Selectfluor (466 mg, 1.25 mmol), $AgNO_3$ (51.0 mg, 0.30 mmol) in acetone:H_2O (7.5mL : 830 µL), heated to 90 °C for 16 h in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc to afford **113b** as a pale yellow oil (112 mg, 45%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 1.7 Hz, 1H), 7.60 (dt, *J* = 7.9 Hz, 0.88 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.8, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 136.6, 134.7, 130.4, 124.8, 94.6, 77.5, 69.8, 25.4.

S4.4.3. Nucleophilic substitution products

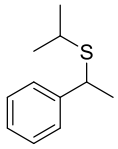
All reactions were carried out in accordance with general procedure F at 0.167 M concentration; the reaction scale, amounts of Selectfluor and respective nucleophiles are specified below. The yields of compounds **92f**, **92i**, **92j**, **92k**, **92u** were calculated via ^{1}H NMR and product identity confirmed by GC-MS. **92f**,**i-k** were not isolated due to volatility and **92u** co-eluted with unreacted *tert*-butyl tosylcarbamate, easier purification could be obtained by treating the crude reaction mixture with TFA to deprotect the unreacted starting material.

(3-Bromobenzyl)(1-phenylethyl)sulfane 92e



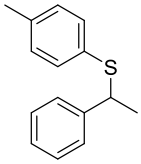
General procedure F was applied with (1-fluoroethyl)benzene **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and (3-bromo)methanethiol (104.7 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 ^{o}C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:DCM to 90:10 hexane:DCM to afford **92e** as colourless oil (59 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 7H), 7.13 – 7.05 (m, 2H), 3.76 (q, *J* = 7.1 Hz, 1H), 3.39 (ABq, *J* = 25.0, 13.7 Hz, 2H), 1.49 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 141.0, 132.0, 130.1, 130.0, 128.7 (2C), 127.6 (2C), 127.4, 122.4, 43.9, 35.4, 22.7. IR: *ν*max (cm^{-1}) = 2968 (C−H), 1567 (C=C aryl), 1450 (C=C aryl), 1116 (C−Br aryl), 783 (C−H m-disub benzene), 698 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{15}H_{15}BrS$: $[M+H]^+$ = 307.0151; found = 307.0158.

Isopropyl(1-phenylethyl)sulfane 92f



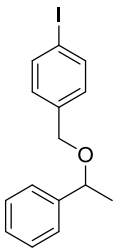
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and propane-2-thiol (19 μL, 0.20 mmol) in MeCN (0.60 mL, 0.167 M), heated to 90 ^{o}C for 30 min in a 10 mL crimp cap vial. The yield of **92f** was determined by ^{1}H NMR analysis using trimethoxybenzene as the internal standard (81%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 7.26 – 7.17 (m, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 2.63 (sept, *J* = 6.7 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H).

(1-Phenylethyl)(*p*-tolyl)sulfane 92g[305]



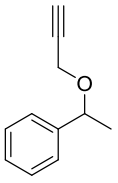
General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and *p*-tolylbenzenethiol (63.4 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 95:5 hexane:Et_2O to afford **92g** as colourless oil (55 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.12 (m, 7H), 7.00 (d, *J* = 7.9 Hz, 2H), 4.24 (q, *J* = 7.0 Hz, 1H), 2.26 (s, 3H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 137.3, 133.2 (2C), 131.3, 129.4 (2C), 128.3 (2C), 127.3 (2C), 127.0, 48.4, 22.2, 21.1.

1-Iodo-4-((1-phenylethoxy)methyl)benzene 92h



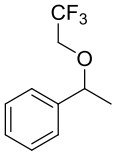
General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and *p*-iodobenzylalcohol (120.7 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 90:10 hexane:Et_2O to afford **92h** as a yellow oil (68 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.42 – 7.27 (m, 5H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.32 (dd, *J* = 53.3, 12.1 Hz, 2H), 1.49 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 138.5, 137.6, 129.7, 128.7, 127.8, 126.4, 93.0, 69.7, 24.3. IR: *ν*max (cm^{-1}) = 2973 (C−H), 1484 (C=C aryl), 1450 (C=C aryl), 1089 (C−O), 832 (C−H *p*-disub benzene), 760 (C−H monosub benzene), 699 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{15}H_{15}IO$ $[M+NH_4]^+$ = 356.0506; found = 356.0507.

(1-(Prop-2-ynyloxy)ethyl)benzene 92i[306]



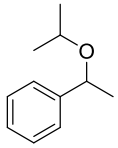
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and propargyl alcohol (12 μL, 0.20 mmol) in MeCN (0.60 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The yield of **92i** was determined by ^{1}H NMR analysis using trimethoxybenzene as the internal standard (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.65 (q, *J* = 6.5 Hz, 1H), 4.06 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.89 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.54 (t, *J* = 2.4 Hz, 1H), 1.45 (d, *J* = 6.5 Hz, 3H).

(1-(2,2,2-Trifluoroethoxy)ethyl)benzene 92j[307]



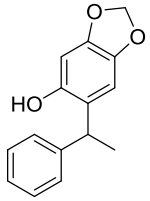
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and 2,2,2-trifluroethanol (12 μL, 0.20 mmol) in MeCN (0.60 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The yield of **92j** was determined by ^{1}H NMR analysis using trimethoxybenzene as the internal standard (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 4.60 (q, *J* = 6.3 Hz, 1H), 3.74 – 3.64 (m, 2H), 1.48 (d, *J* = 6.3 Hz, 3H).

(1-Isopropoxyethyl)benzene 92k[308]



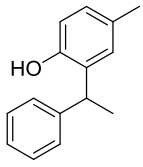
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and *iso*-propyl alcohol (15 µL, 0.20 mmol) in MeCN (0.60 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The yield of **92k** was determined by ^{1}H NMR analysis using trimethoxybenzene as the internal standard (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 5H), 4.55 (q, *J* = 6.5 Hz, 1H), 3.50 (sept, *J* = 6.4 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H).

6-(1-Phenylethyl)benzo[d][1,3]dioxol-5-ol 92n



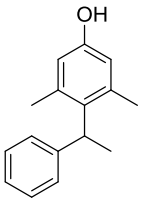
General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and sesamol (70.5 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 80:20 hexane:EtOAc, then recrystallisation in Hexane:EtOAc to afford **92n** as colourless needles (52 mg, 85%). mp 101-103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 5H), 6.71 (s, 1H), 6.34 (s, 1H), 5.86 (dd, *J* = 3.8, 1.4 Hz, 2H), 4.29 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 1.60 – 1.50 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 146.3, 145.3, 141.7, 128.8 (2C), 127.4 (2C), 126.5, 124.1, 107.4, 101.0, 98.9, 38.6, 21.2. IR: *v*max (cm^{-1}) = 3434 (O−H), 2969 (C−H), 1507 (C=C aryl), 1435 (CH_3), 1241 (C−O aryl ether), 1189 (C−O alkyl ether), 1033 (C-O alcohol), 698 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{15}H_{14}O_3$: $[M+H]^+$ = 243.1016; found = 243.1019.

4-Methyl-2-(1-phenylethyl)phenol 92o[309]



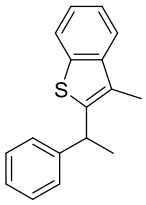
General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and *p*-cresol (55.3 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 90:10 hexane:EtOAc to afford **92o** as a pale yellow oil (35 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 4H), 7.18 – 7.10 (m, 1H), 6.99 (d, *J* = 1.7 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 4.38 (s, 1H), 4.29 (d, *J* = 7.2 Hz, 1H), 2.24 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 145.4, 131.7, 130.0, 128.6 (2C), 128.5, 127.9, 127.5 (2C), 126.4, 115.9, 38.8, 21.0, 20.7.

3,5-Dimethyl-4-(1-phenylethyl)phenol 92p



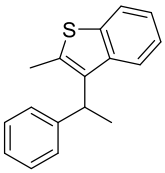
General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and 3,5-dimethylphenol (61.1mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 90:10 hexane:EtOAc to afford **92p** as a pale yellow oil (57 mg, 82%, 95:5 mixture *p*:*o* regioisomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 5.25H), 6.58 (s, 1H), 6.43 (app d, *J* = 2.9 Hz, 0.10H), 6.39 (s, 1H), 4.61 (q, *J* = 7.5 Hz, 0.05H), 4.51 (q, *J* = 7.3 Hz, 1H), 4.34 (s, 1H), 4.27 (d, *J* = 0.9 Hz 0.05H), 2.30 (s, 3H), 2.19 (s, 3H), 1.66 (dd, *J* = 3.6, 7.3 Hz, 0.15H), 1.62 (d, *J* = 7.3 Hz, 3H).). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 144.0, 137.3, 137.0, 129.0 (2C), 128.1, 127.1 (2C), 126.7, 124.2, 116.1, 36.2, 21.0, 20.7, 16.9. IR: *v*max (cm^{-1}) = 3521 (O−H), 2971 (C−H), 1581 (C=C aryl), 1493 (C=C aryl), 1446 (CH_3), 1028 (C-O alcohol), 698 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{15}H_{18}O$: $[M+H]^+$ = 227.1430; found = 227.1429.

3-Methyl-2-(1-phenylethyl)benzo[*b*]thiophene 92q



General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and 3-methylbenzo[b]thiophene (68 µL, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 95:5 hexane:Et_2O to afford **92q** as a pale yellow oil (32 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.13 (m, 7H), 4.56 (q, *J* = 7.2 Hz, 1H), 2.28 (s, 3H), 1.71 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 144.7, 141.1, 138.3, 128.6 (2C), 127.4 (2C), 126.6 (2C), 124.0, 123.7, 122.4, 121.5, 39.1, 22.9, 11.9. IR: *v*max (cm^{-1}) = 2969 (C−H), 1603 (C=C aryl), 1495 (C=C aryl), 1437 (CH_3), 754 (*o,o*-disub benzene), 730 (C−H monosub benzene), 699 (C−H monosub benzene). HRMS +p APCI *m/z* calcd. $C_{17}H_{16}S$: $[M+H]^+$ = 253.1045; found = 253.1048.

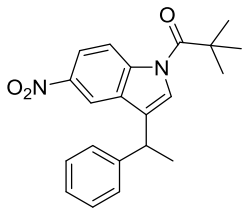
2-Methyl-3-(1-phenylethyl)benzo[*b*]thiophene 92r



General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and 2-methylbenzo[b]thiophene (75.6 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was purified by FCC eluting a gradient of 100% hexane to 92:8 hexane:DCM to afford **92r** as a yellowish oil (50 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (dd, *J* = 1.3, 7.3 Hz , 1H), 7.40 – 7.36 (m, 1H), 7.30 – 7.21 (m, 4H), 7.19 – 7.10 (m, 3H), 4.61 (q, *J* = 7.3 Hz, 1H), 2.43 (s, 3H), 1.74 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 139.8, 138.6, 135.3, 134.8, 128.4 (2C), 127.4 (2C), 126.0, 123.7, 123.2, 122.5, 122.2, 36.5, 18.5, 14.6. IR: *v*max (cm^{-1}) = 2970 (C−H), 1601 (C=C aryl),

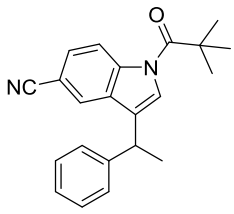
1494 (C=C aryl), 1434 (CH_3), 759 (*o,o*-disub benzene), 731 (C−H monosub benzene), 697 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{17}H_{16}S$: $[M+H]^+$ = 253.1045; found = 253.1048.

5-Nitro-3-(1-phenylethyl)-1-pivaloylindole 92s



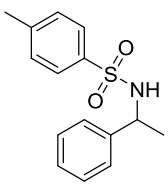
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and 5-nitro-1-pivaloylindole[310] (49.3 mg, 0.20 mmol) in MeCN (0.6 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was recrystallised in hexane:EtOAc the solid was washed with Et_2O and filtrate concentrated in *vacuo* and purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 90:10 hexane: EtOAc to afford **92s** as a white amorphous solid (18 mg, 51%). mp 112-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 9.9 Hz, 1H), 8.20 – 8.16 (m, 2H), 7.63 (d, *J* = 1.0 Hz, 1H), 7.36 – 7.22 (m, 5H), 4.35 (q, *J* = 7.1 Hz, 1H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 144.2, 144.1, 140.8, 129.1, 129.0 (2C), 127.3 (2C), 127.2, 127.1, 125.1, 120.5, 117.6, 115.7, 41.5, 36.7, 28.7 (3C), 21.9. IR: *v*max (cm^{-1}) = 2978 (C−H), 1691 (C=O), 1518 (NO_2 aryl), 1444 (CH_3), 1342 (NO_2 aryl), 805 (C−H 1,2,4-trisub benzene), 741 (C−H monosub benzene), 699 (C−H monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{21}H_{22}O_3N_2$: $[M+H]^+$ = 351.1703; found = 351.1706.

5-Cyano-3-(1-phenylethyl)-1-pivaloylindole 92t



General procedure F was applied with **92a** (31.0 mg, 0.25 mmol), Selectfluor (4.7 mg, 0.0125 mmol) and 5-cyano-1-pivaloylindole[310] (113 mg, 0.50 mmol) in MeCN (1.5 mL, 0.167 M), heated to 90 °C for 30 min in a 10 mL crimp cap vial. The crude was recrystallised in EtOH, the solid was washed with Et_2O and filtrate concentrated in *vacuo* and purified by FCC eluting a gradient of 98:2 hexane:EtOAc to 90:10 hexane: EtOAc to afford **92t** as a pale yellow amorphous solid (45 mg, 54%). mp 98-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.6 Hz, 1H), 7.64 (s, 1H), 7.59 – 7.52 (m, 2H), 7.37 – 7.30 (m, 2H), 7.28 – 7.23 (m, 3H), 4.29 (q, *J* = 7.0 Hz, 1H), 1.73 (d, *J* = 7.1 Hz, 3H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 144.3, 139.6, 129.1, 129.0 (2C), 128.4, 127.3 (2C), 127.0, 126.2, 124.4, 124.3, 119.8, 118.3, 106.7, 41.5, 36.7, 28.7 (3C), 21.9. IR: *v*max (cm^{-1}) = 2973 (C−H), 2221 (C≡N), 1697 (C=O), 1460 (C=C aryl), 809 (C−H 1,2,4-trisub benzene), 704 (monosub benzene). HRMS +*p* APCI *m/z* calcd. $C_{22}H_{22}O_3N_2$: $[M+H]^+$ = 331.1085; found = 331.1810.

4-Methyl-N-(1-phenylethyl)benzenesulfonimide 92u[311]

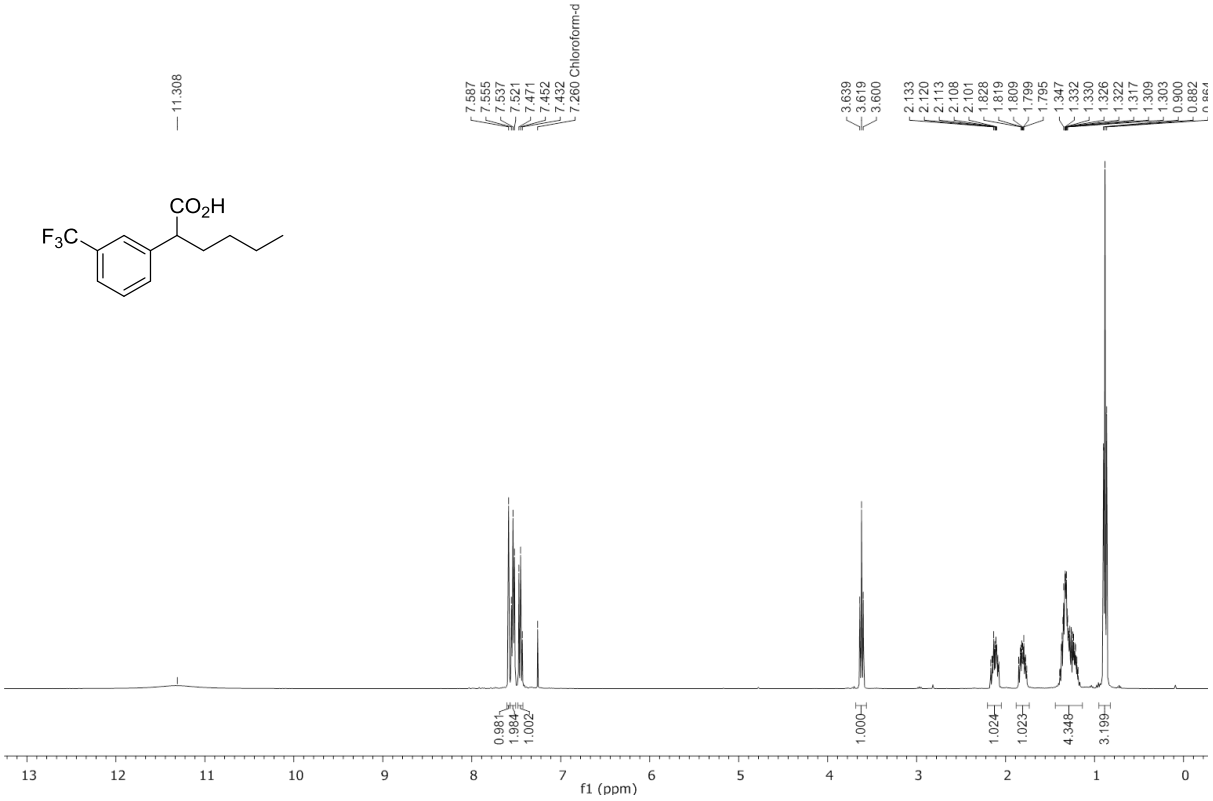


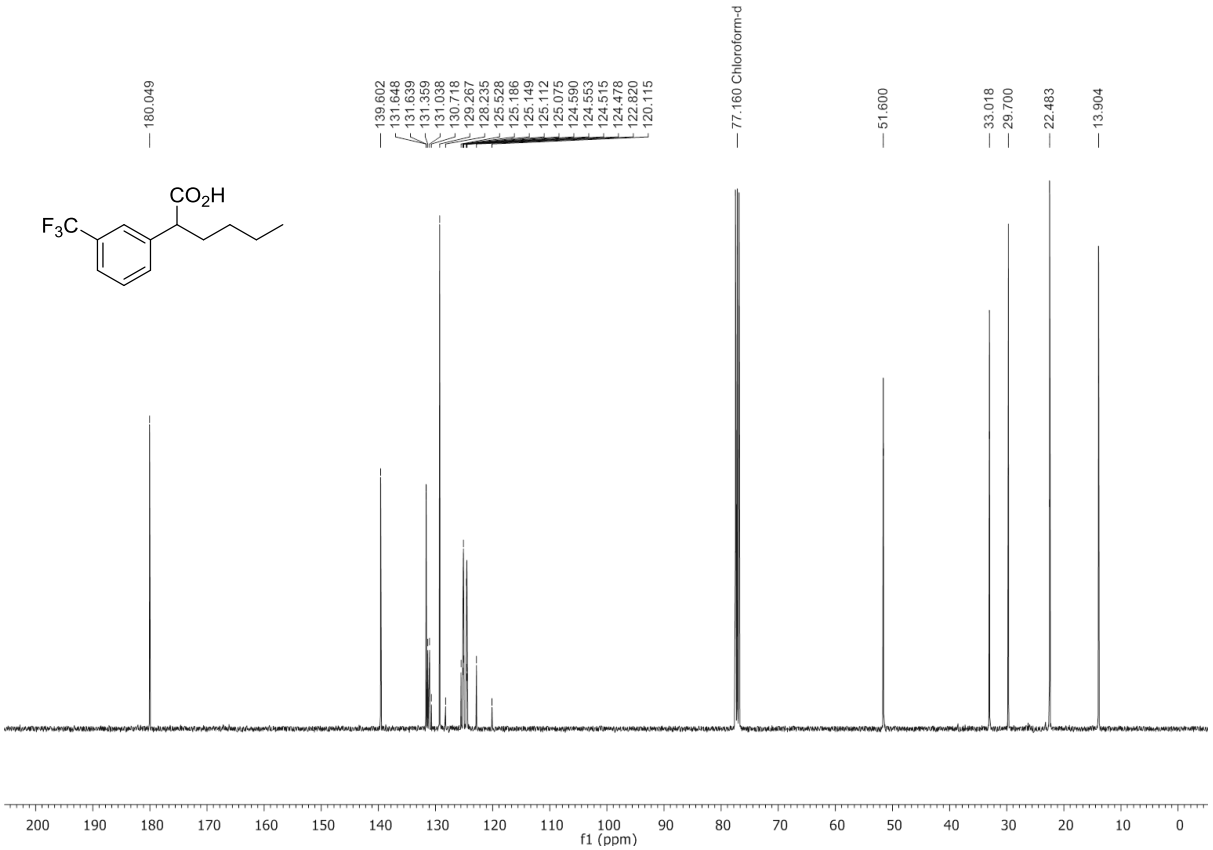
General procedure F was applied with **92a** (12.4 mg, 0.10 mmol), Selectfluor (1.9 mg, 0.005 mmol) and *tert*-butyl tosylcarbamate (51 mg, 0.20 mmol) in MeCN (0.60 mL, 0.167 M), heated to 90 ^{o}C for 30 min in a 10 mL crimp cap vial. The yield of **92u** was determined by ^{1}H NMR analysis using mesitylene as the internal standard (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.21 – 7.11 (m, 5H), 7.11 – 7.01 (m, 2H), 4.85 (d, *J* = 6.8 Hz, 1H, NH), 4.44 (quin, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.40 (d, *J* = 6.9 Hz, 3H).

S4.5. SPECTRA FOR NEW COMPOUNDS

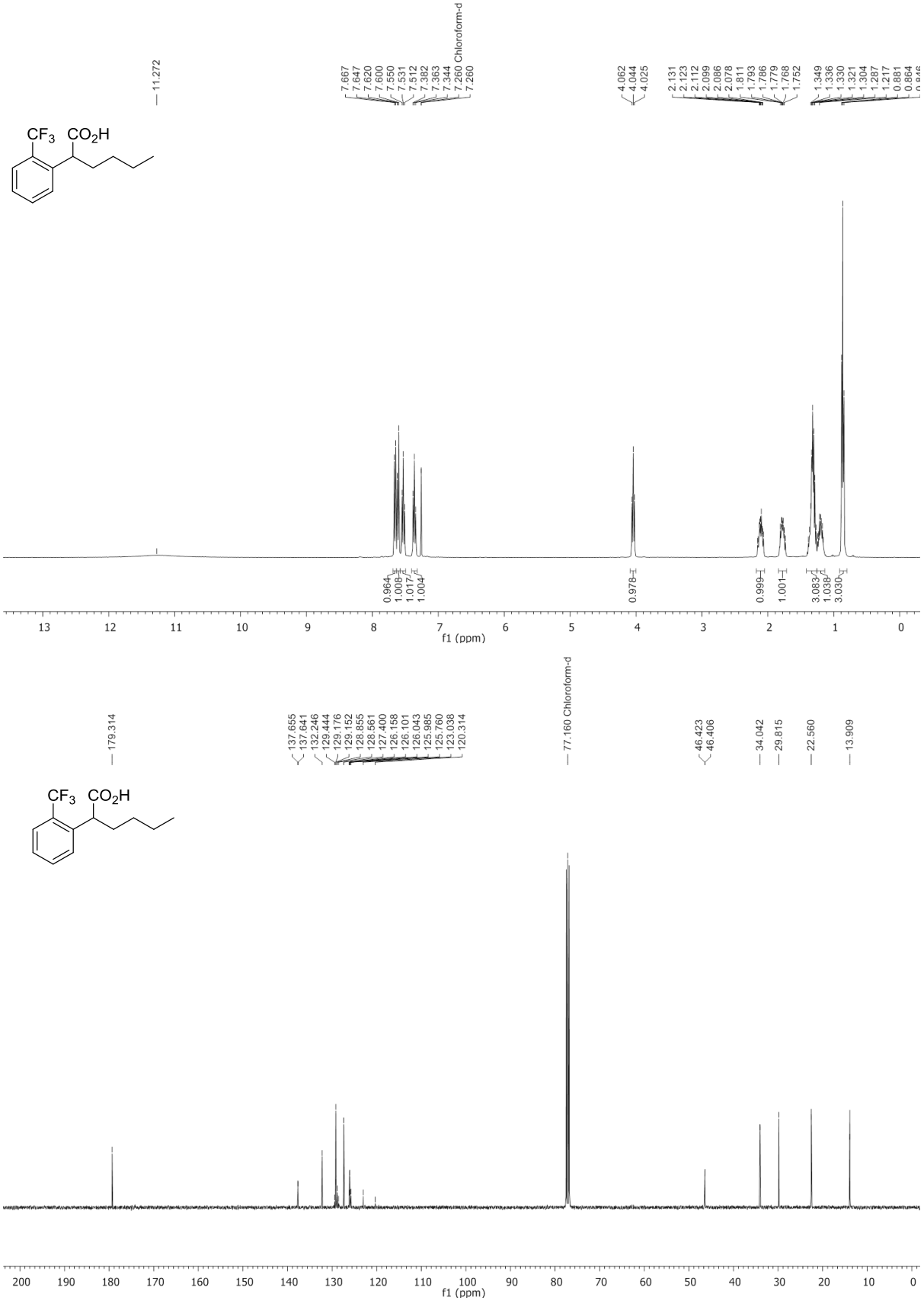
S4.5.1. Starting materials

2-(3-(Trifluoromethyl)phenyl)hexanoic acid **110**



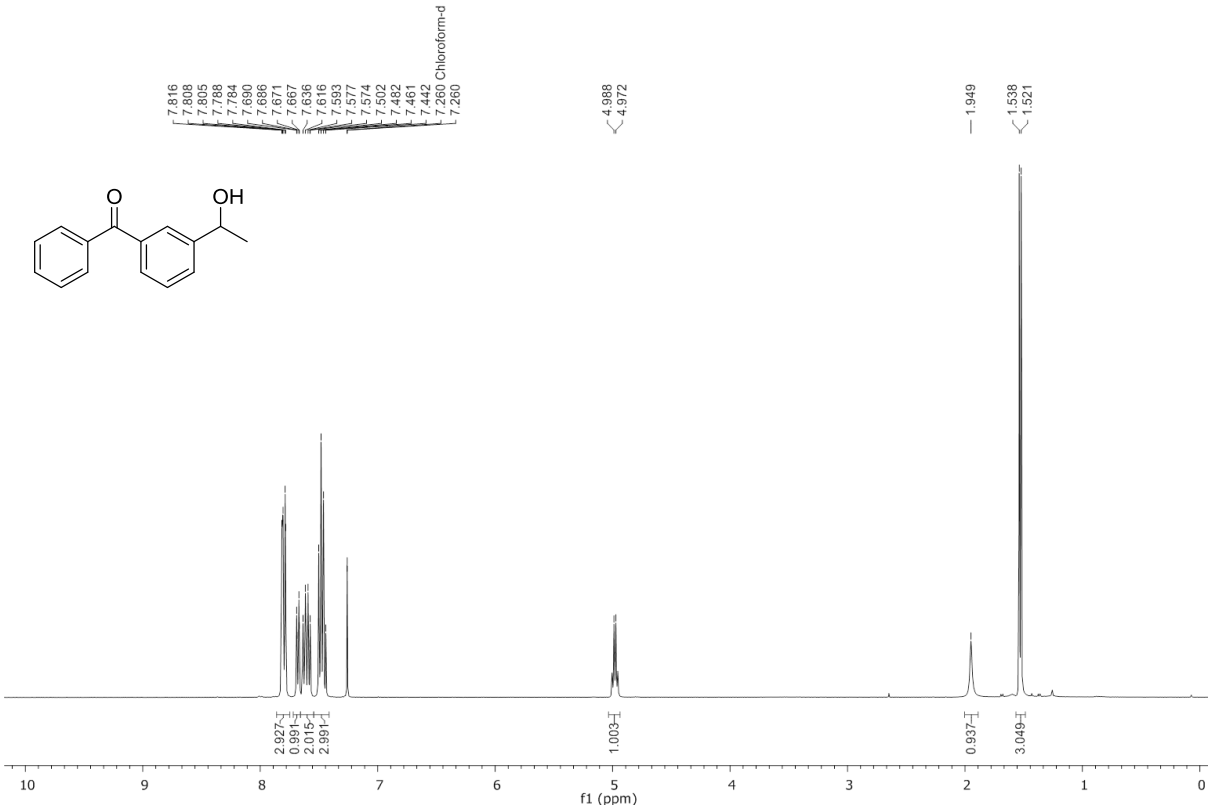


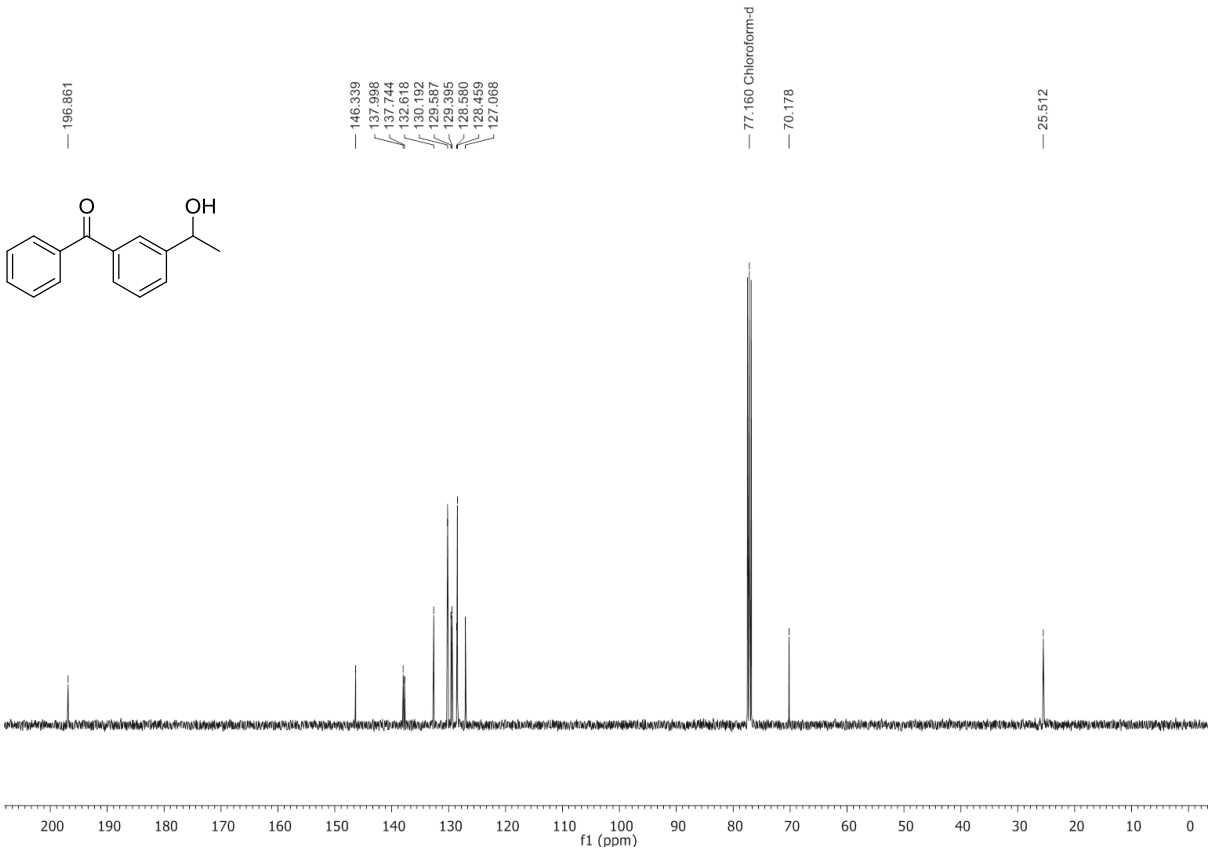
2-(2-(Trifluoromethyl)phenyl)hexanoic acid **114**



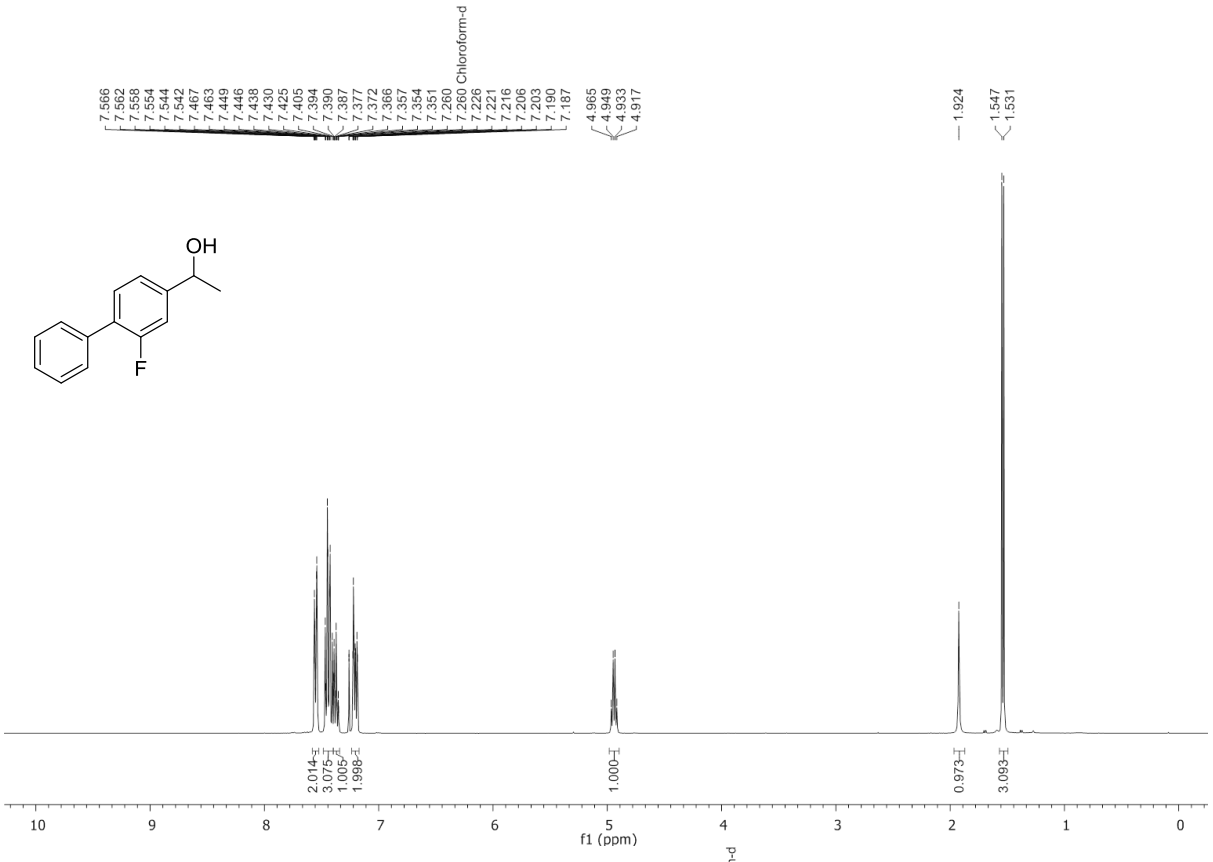
S4.5.2. Benzylic alcohols

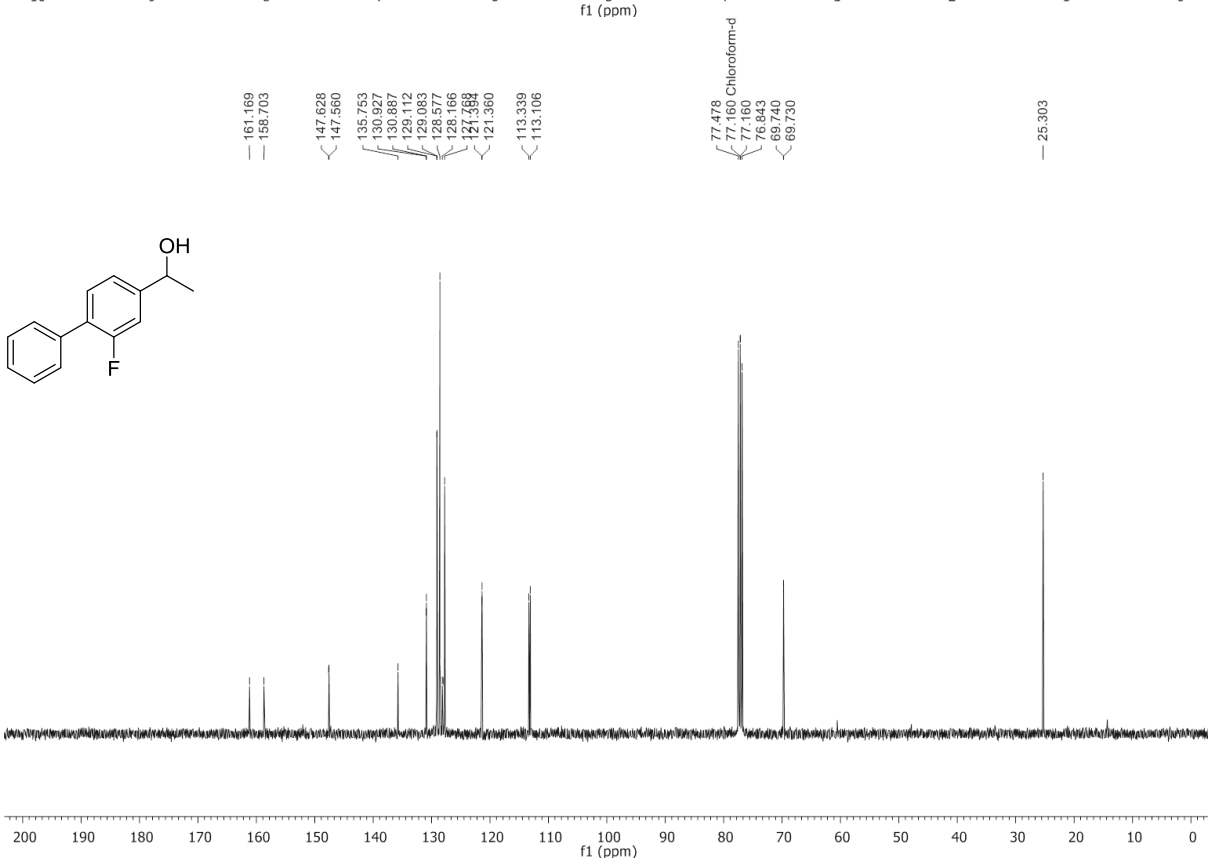
(3-(1-Hydroxyethyl)phenyl)(phenyl)methanone **95b**



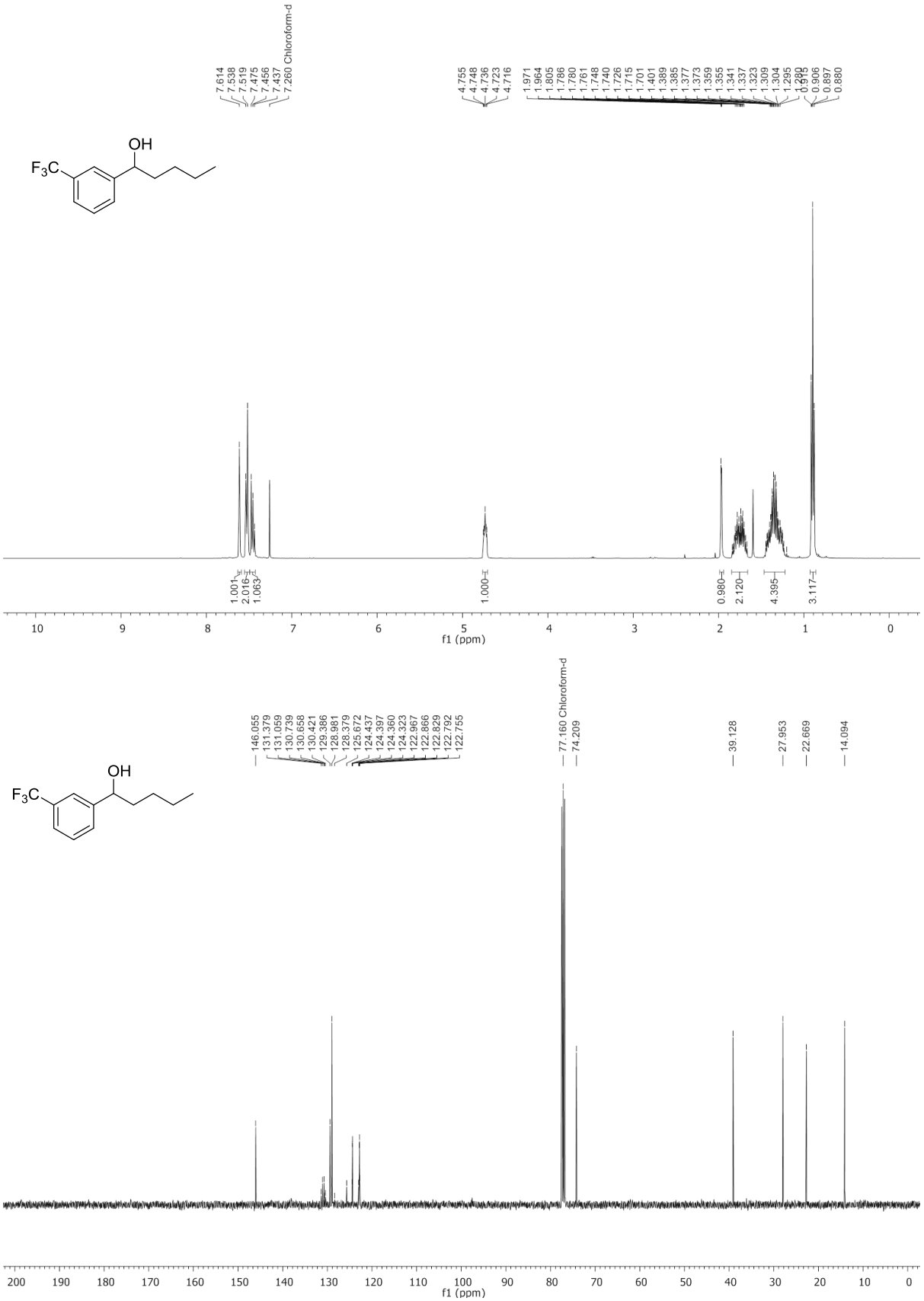


1-(2-Fluoro-[1,1'-biphenyl]-4-yl)ethan-1-ol **96b**



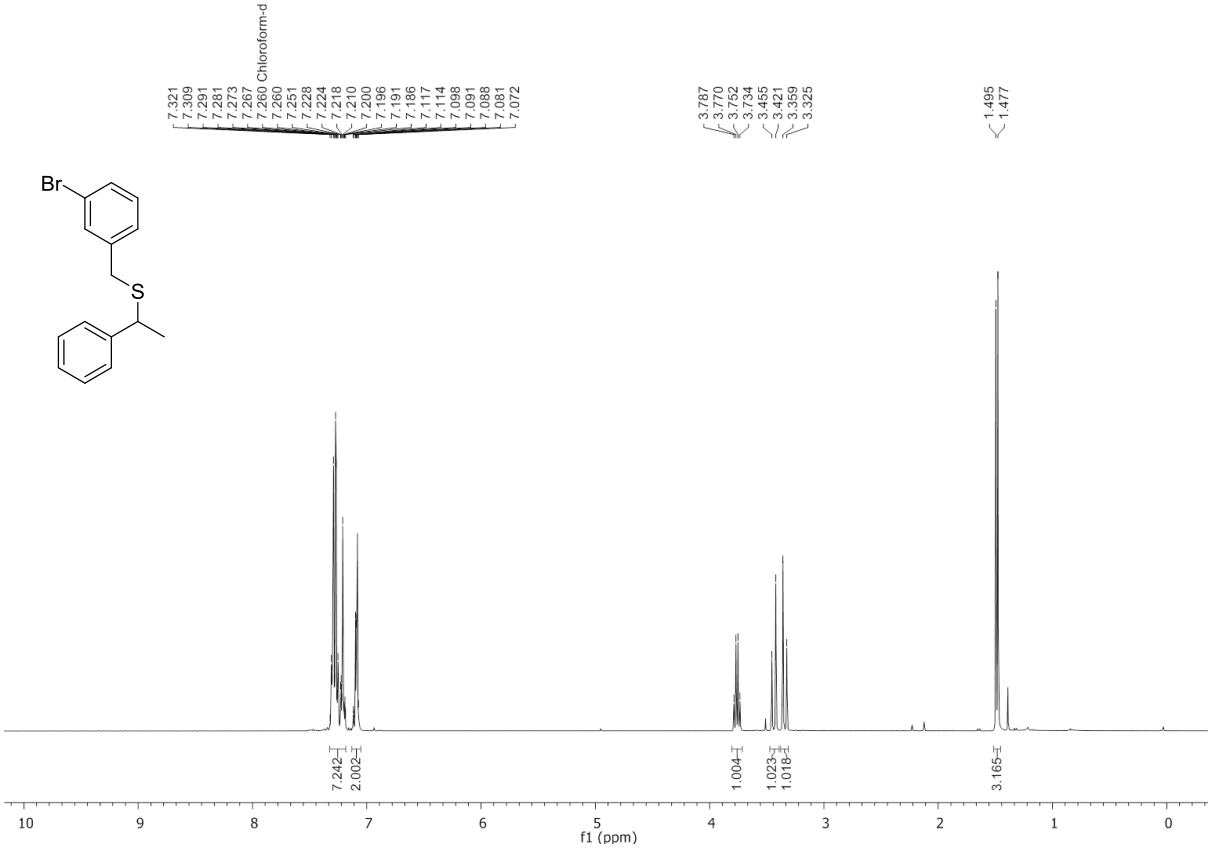


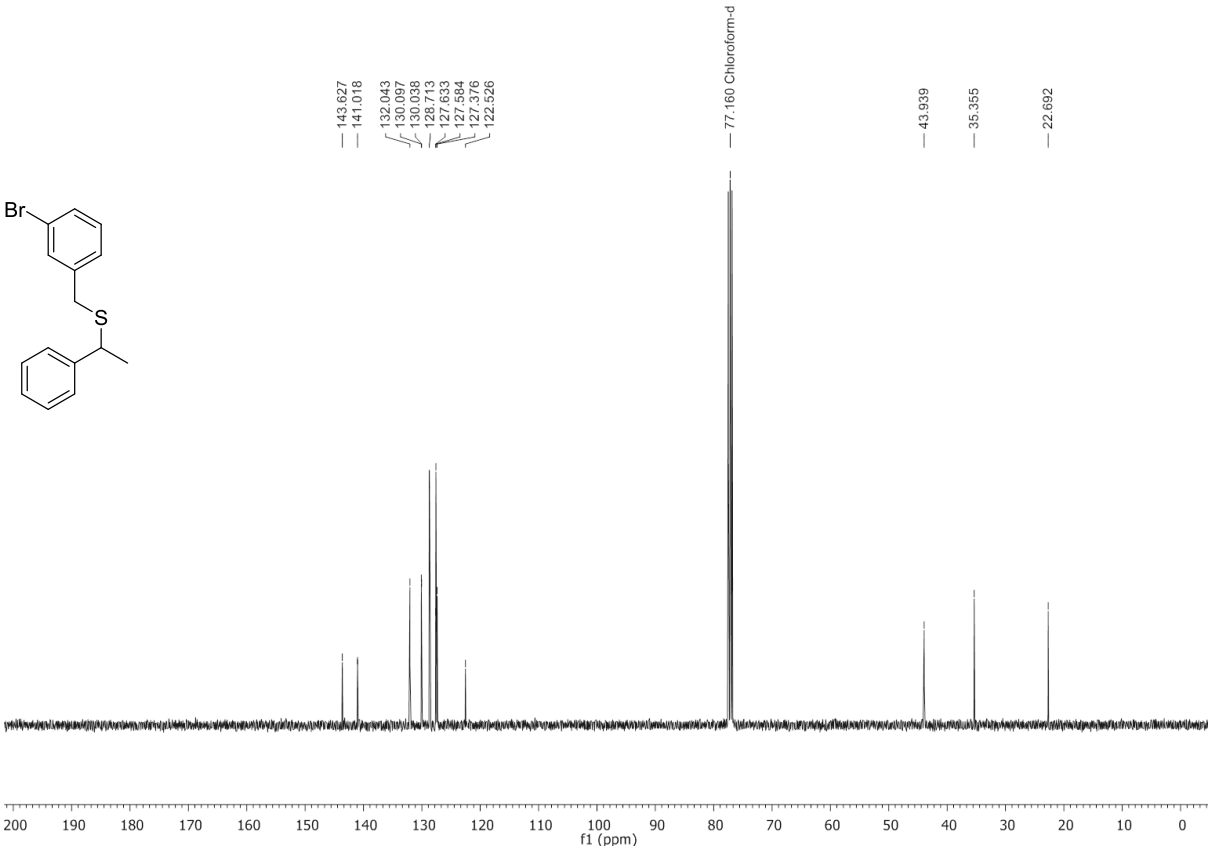
1-(3-(Trifluoromethyl)phenyl)pentan-1-ol **110b**



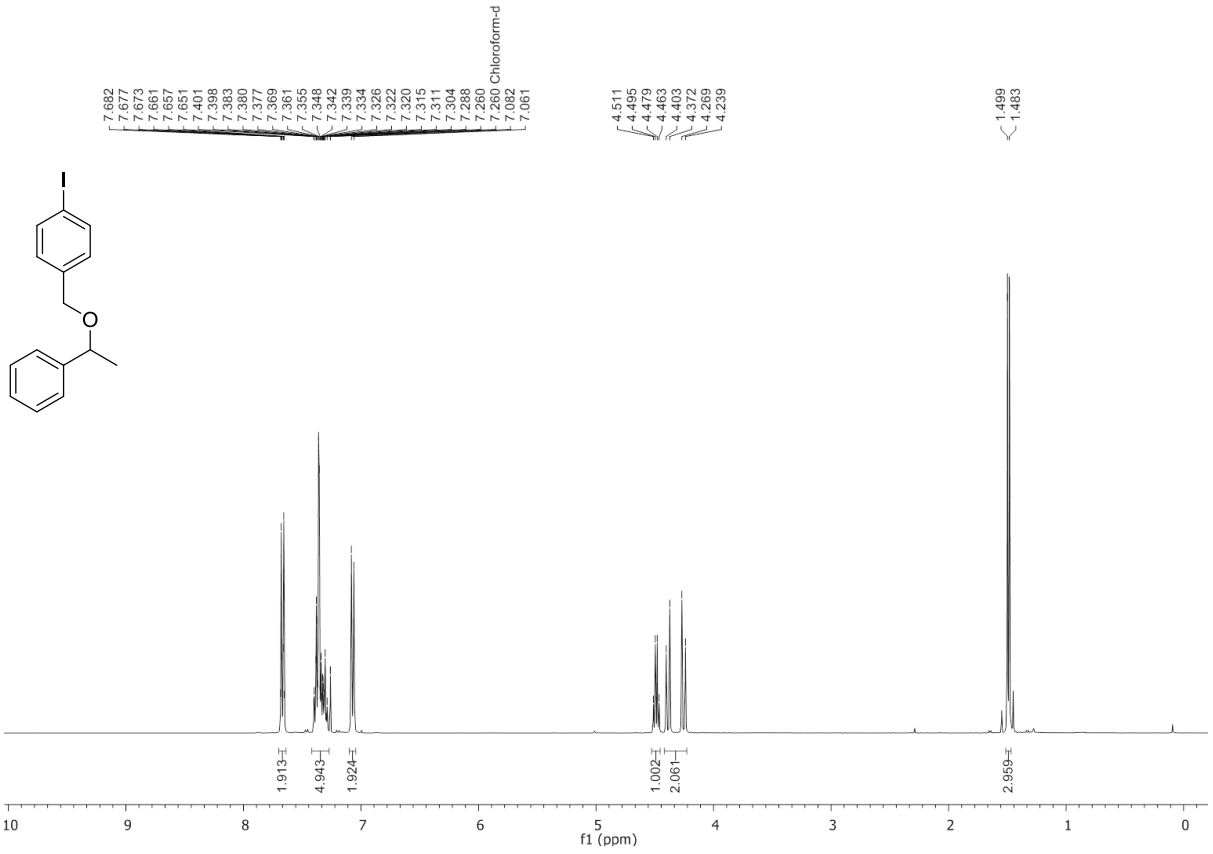
S4.5.3. Nucleophilic substitution products

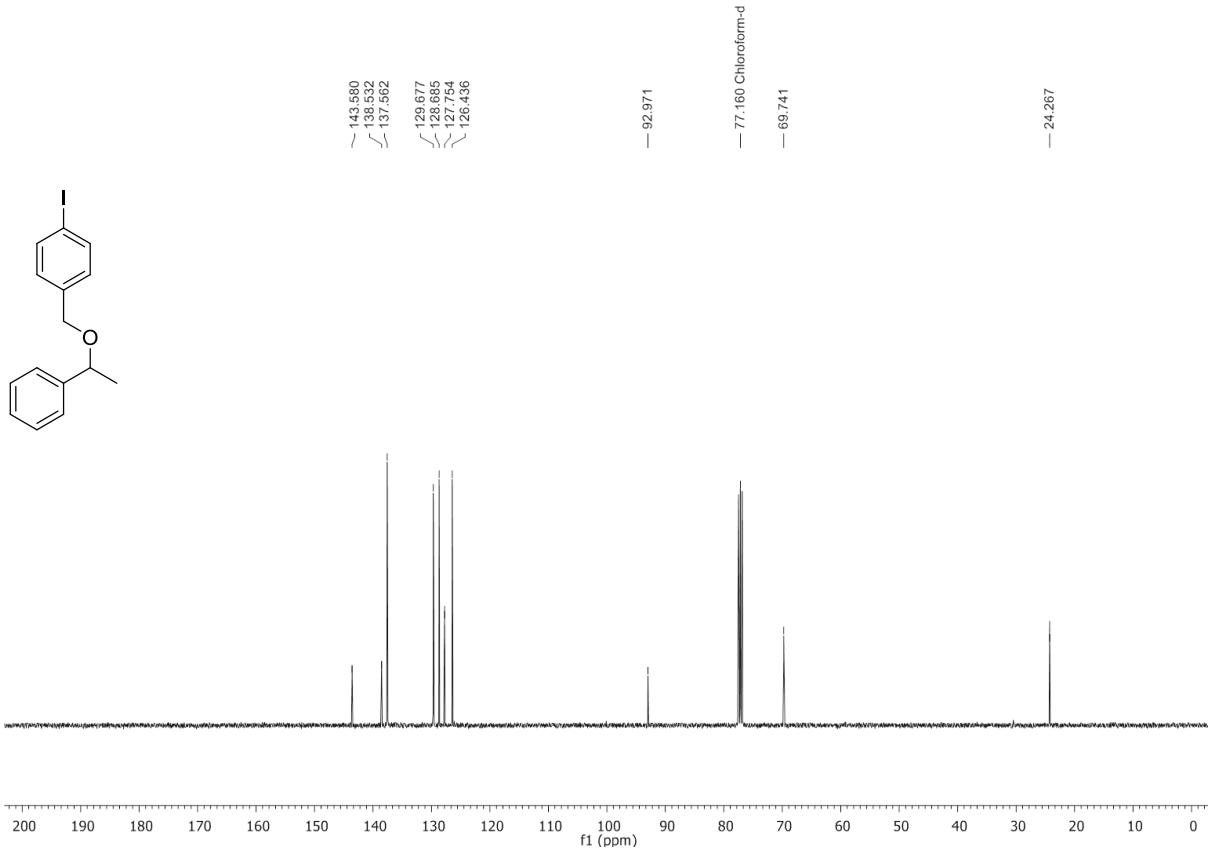
(3-Bromobenzyl)(1-phenylethyl)sulfane **92e**



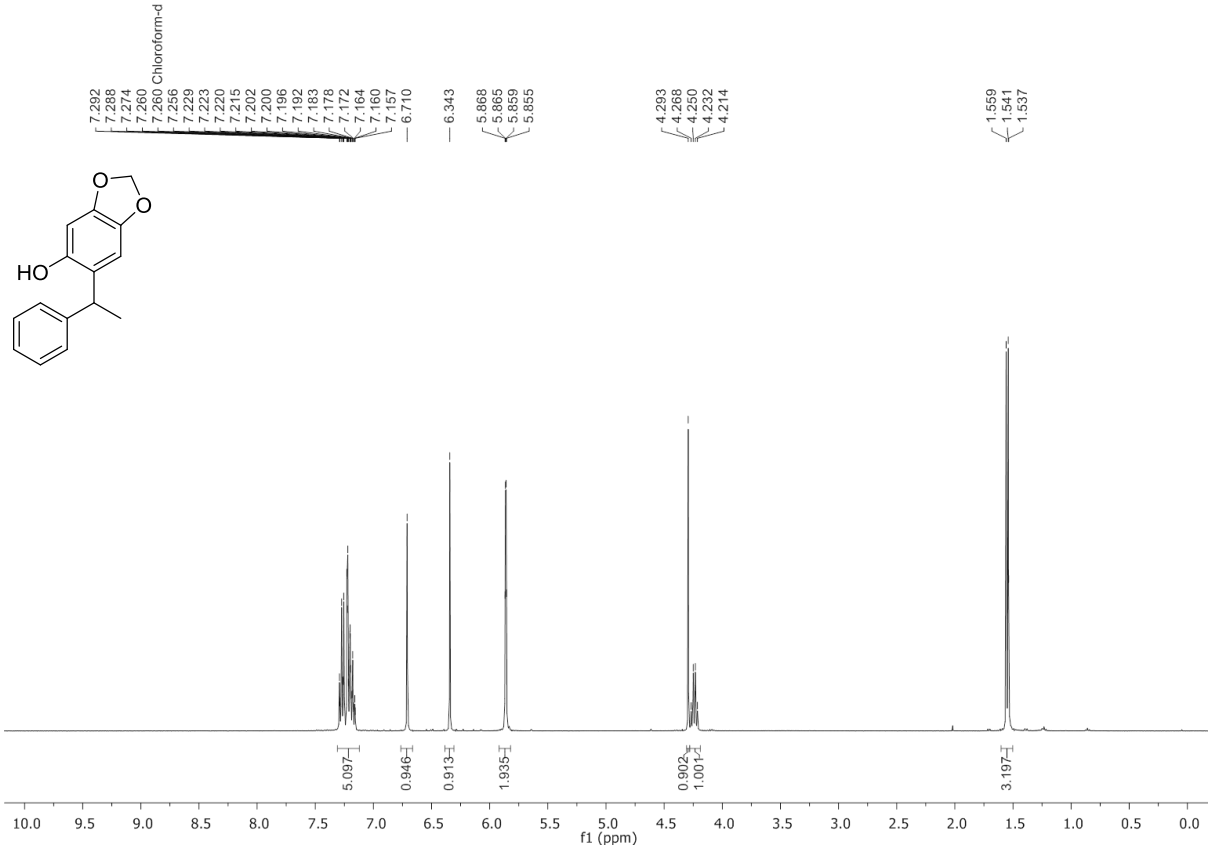


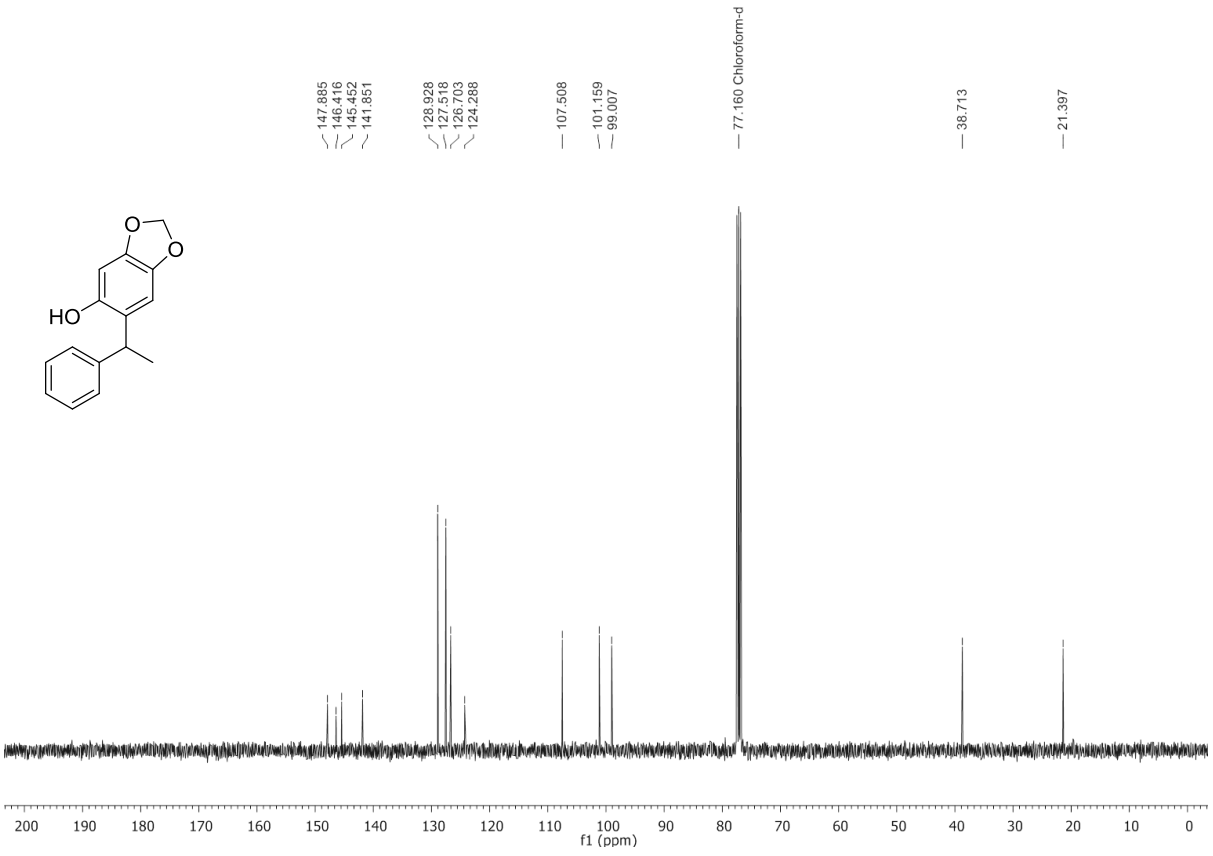
1-Iodo-4-((1-phenylethoxy)methyl)benzene **92h**



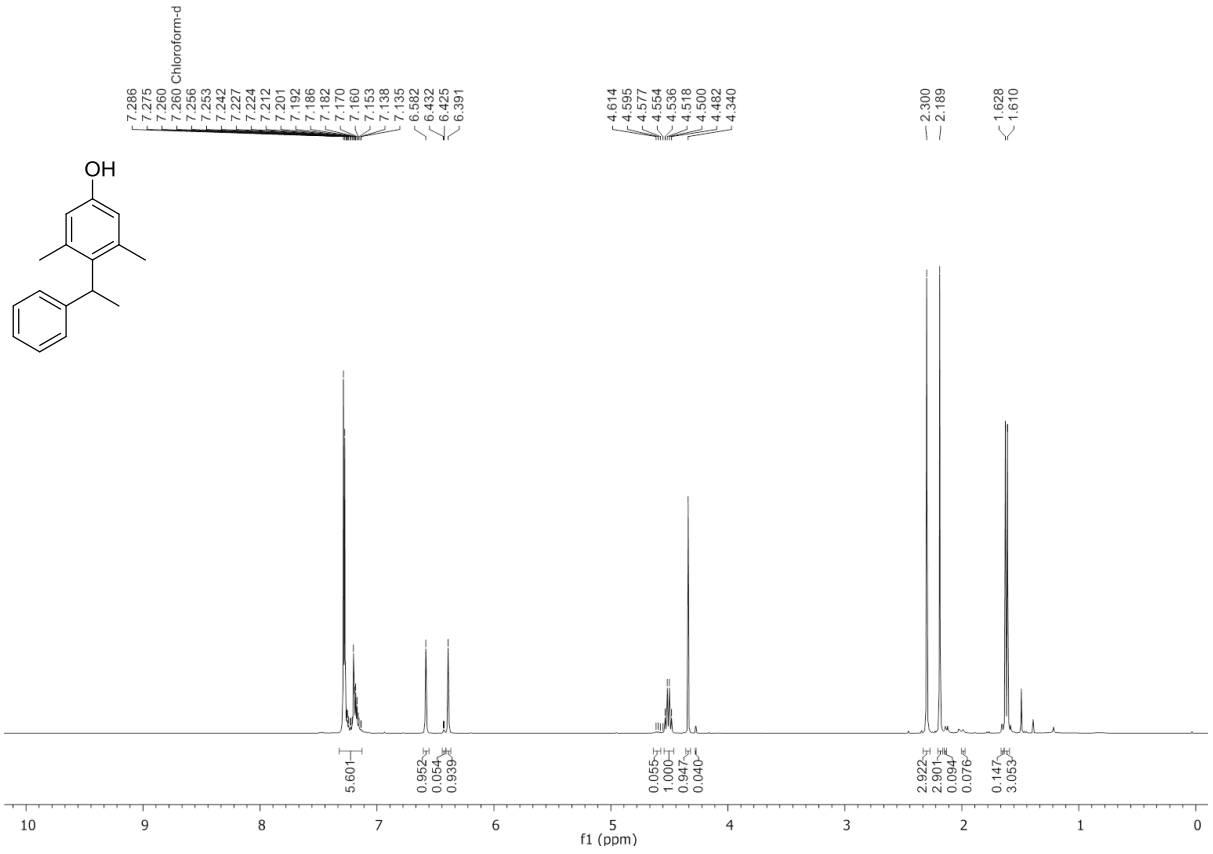


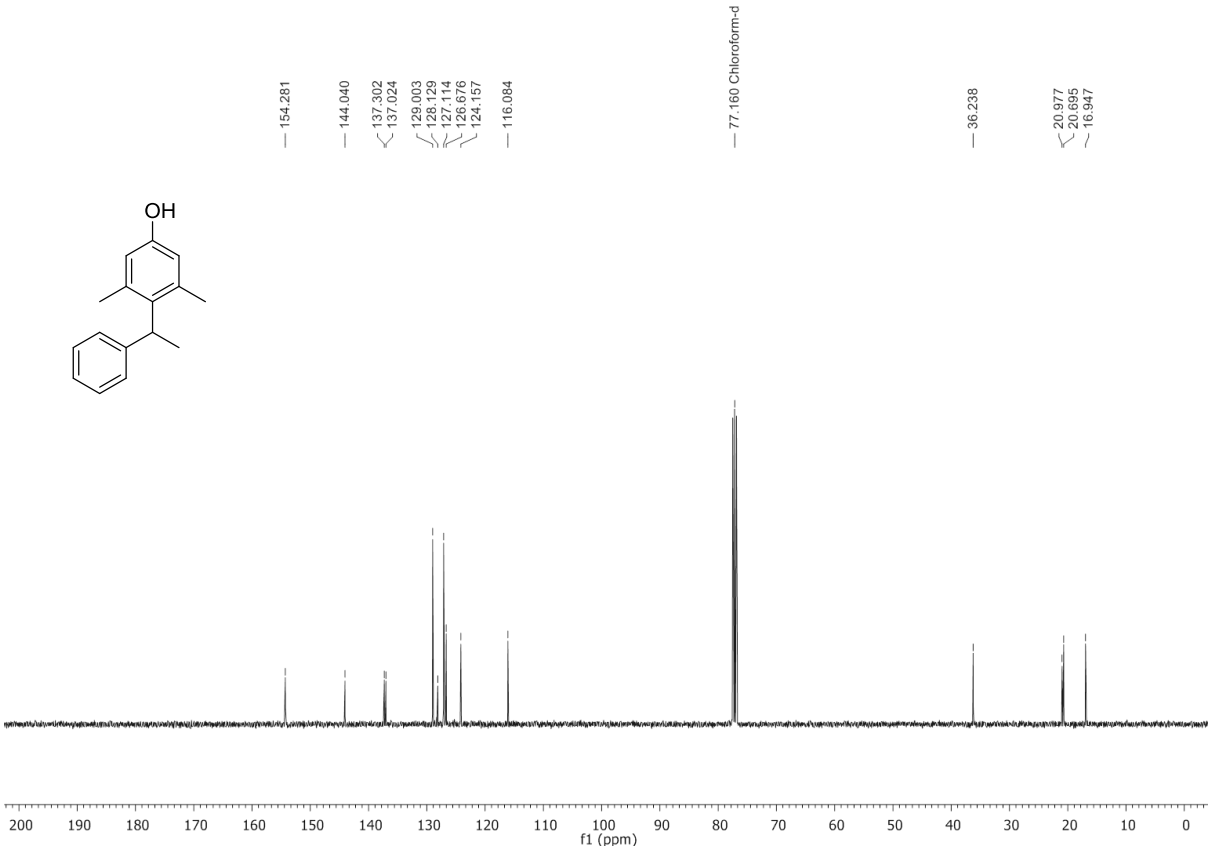
6-(1-Phenylethyl)benzo[d][1,3]dioxol-5-ol **92n**



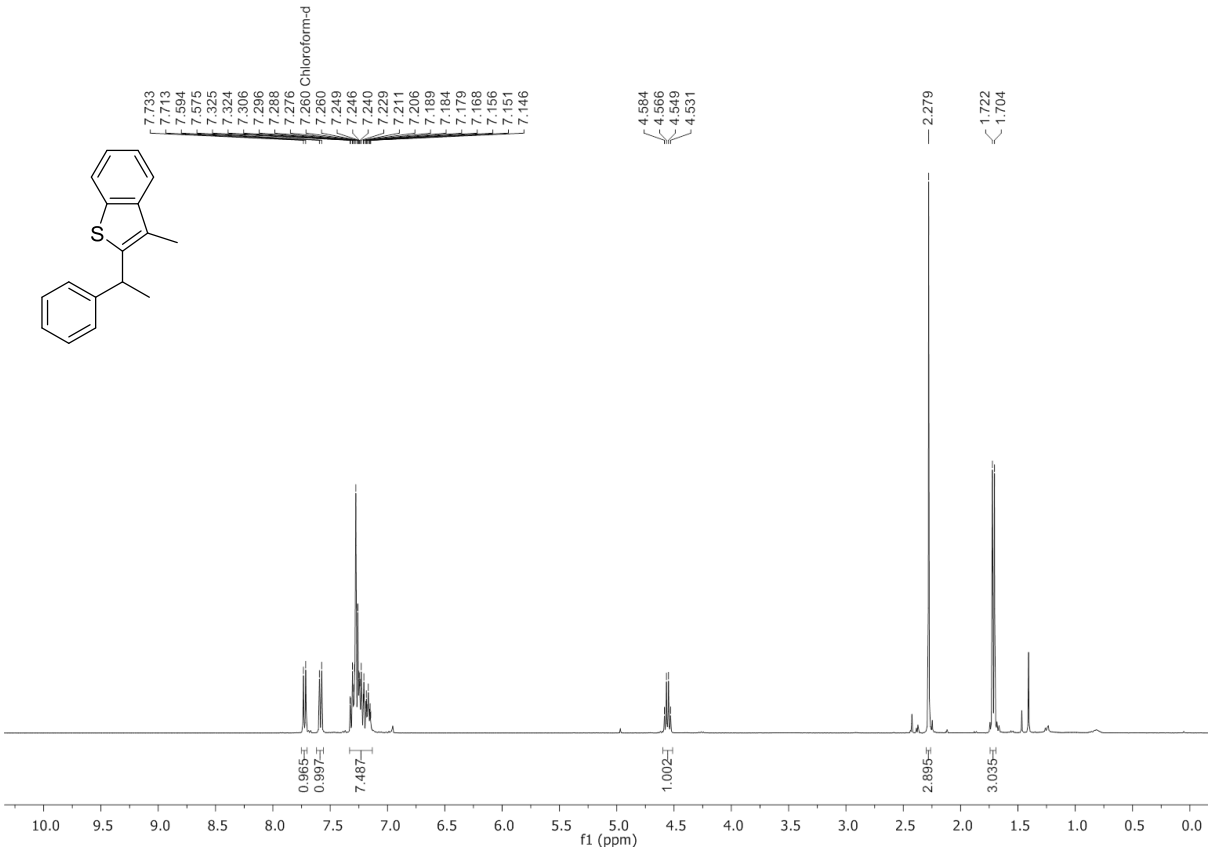


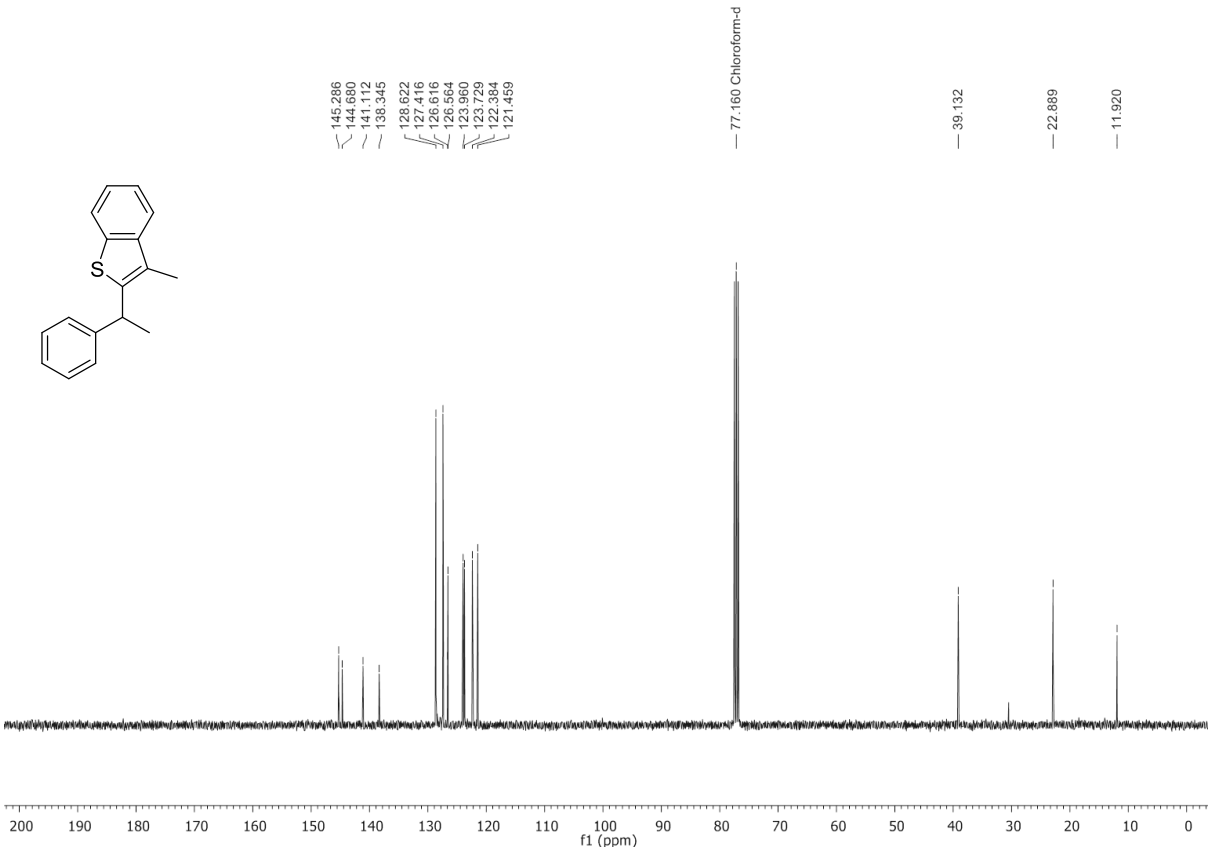
3,5-Dimethyl-4-(1-phenylethyl)phenol **92p**



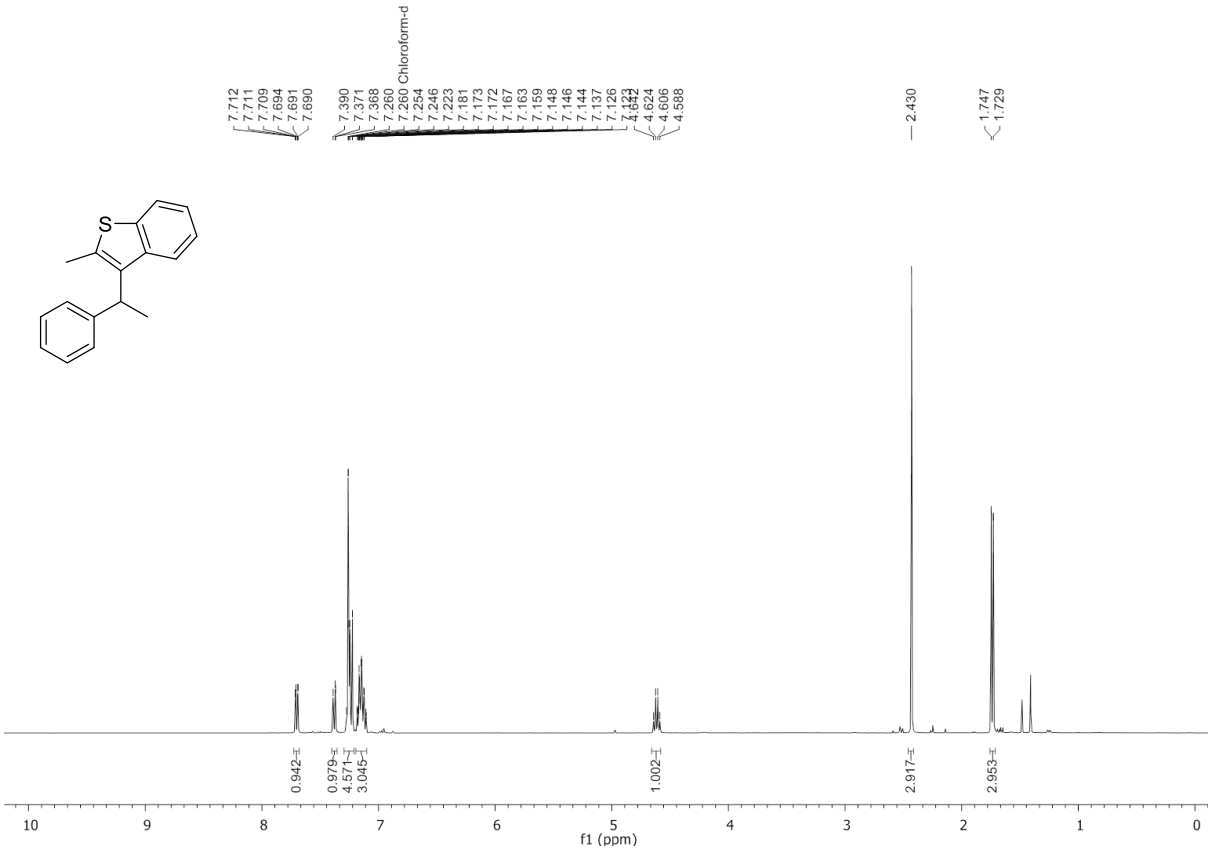


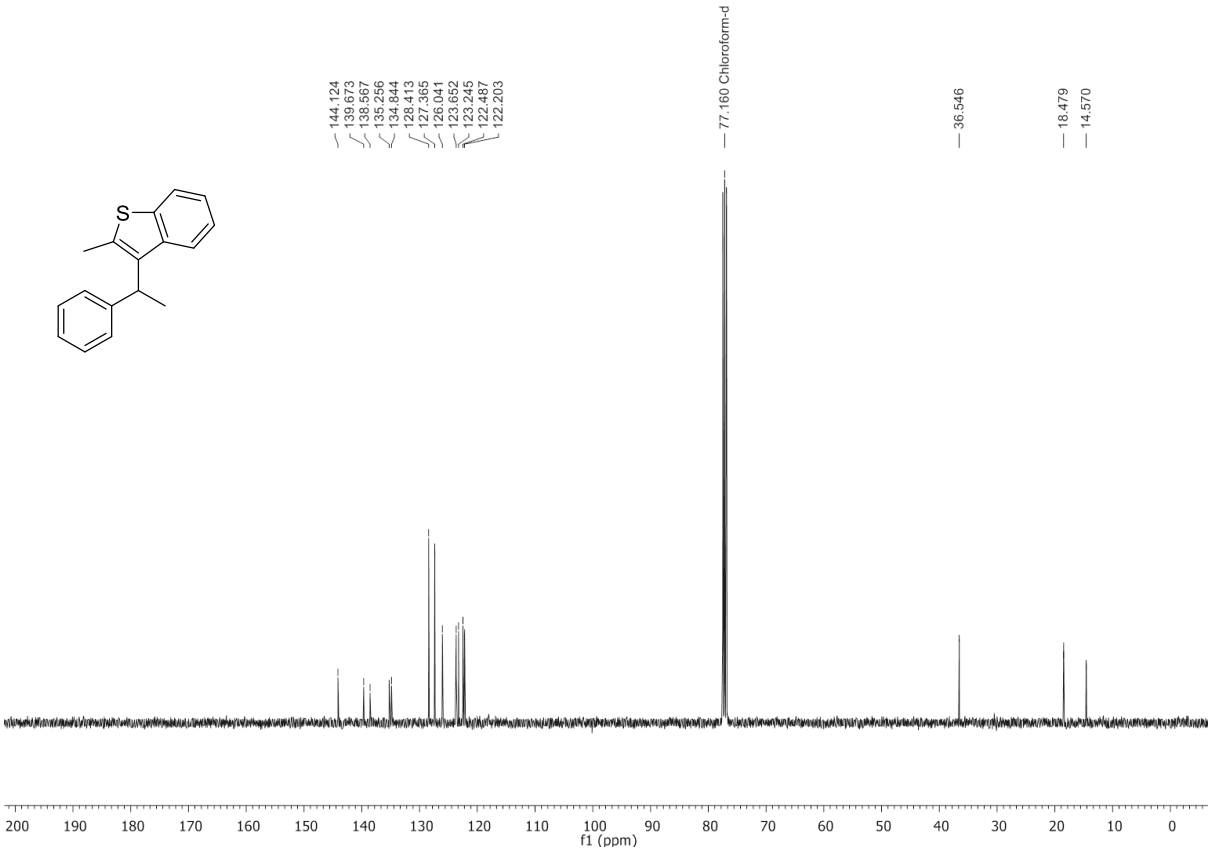
3-Methyl-2-(1-phenylethyl)benzo[b]thiophene **92q**



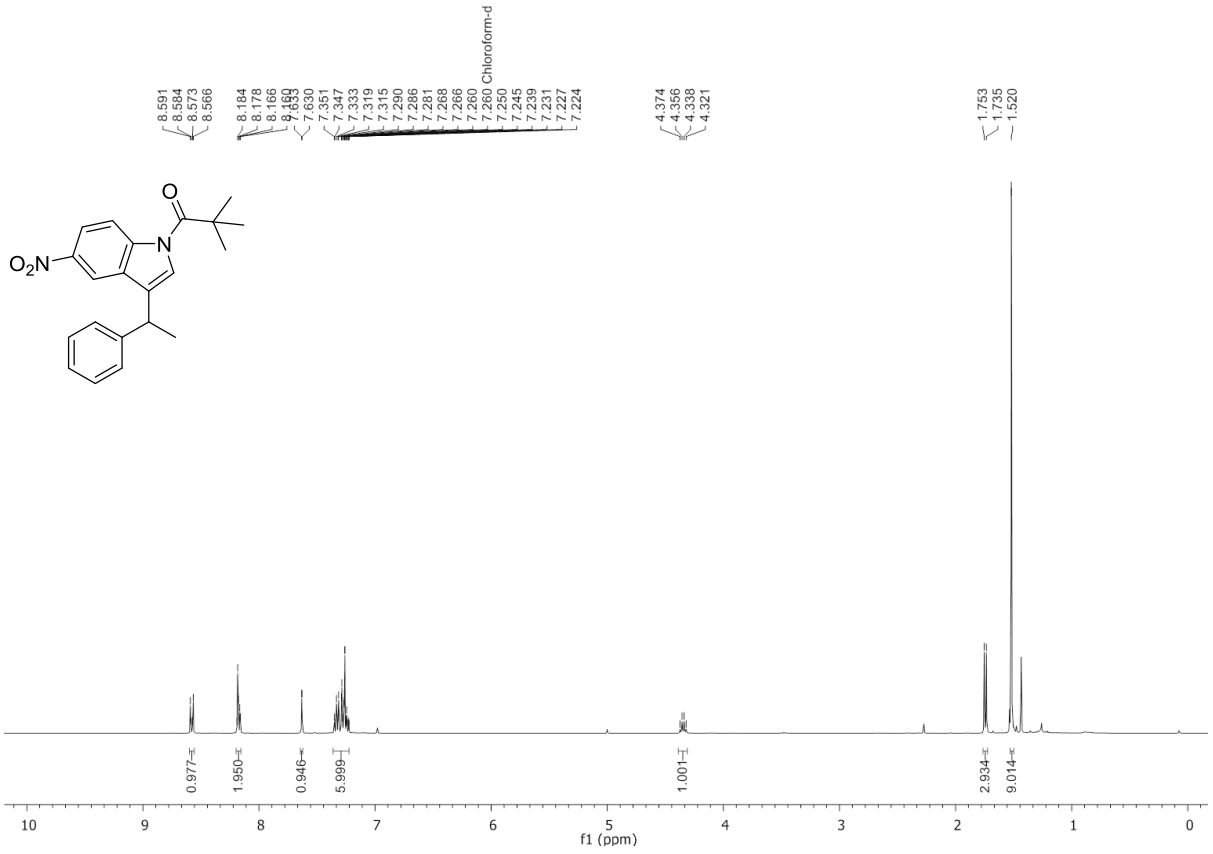


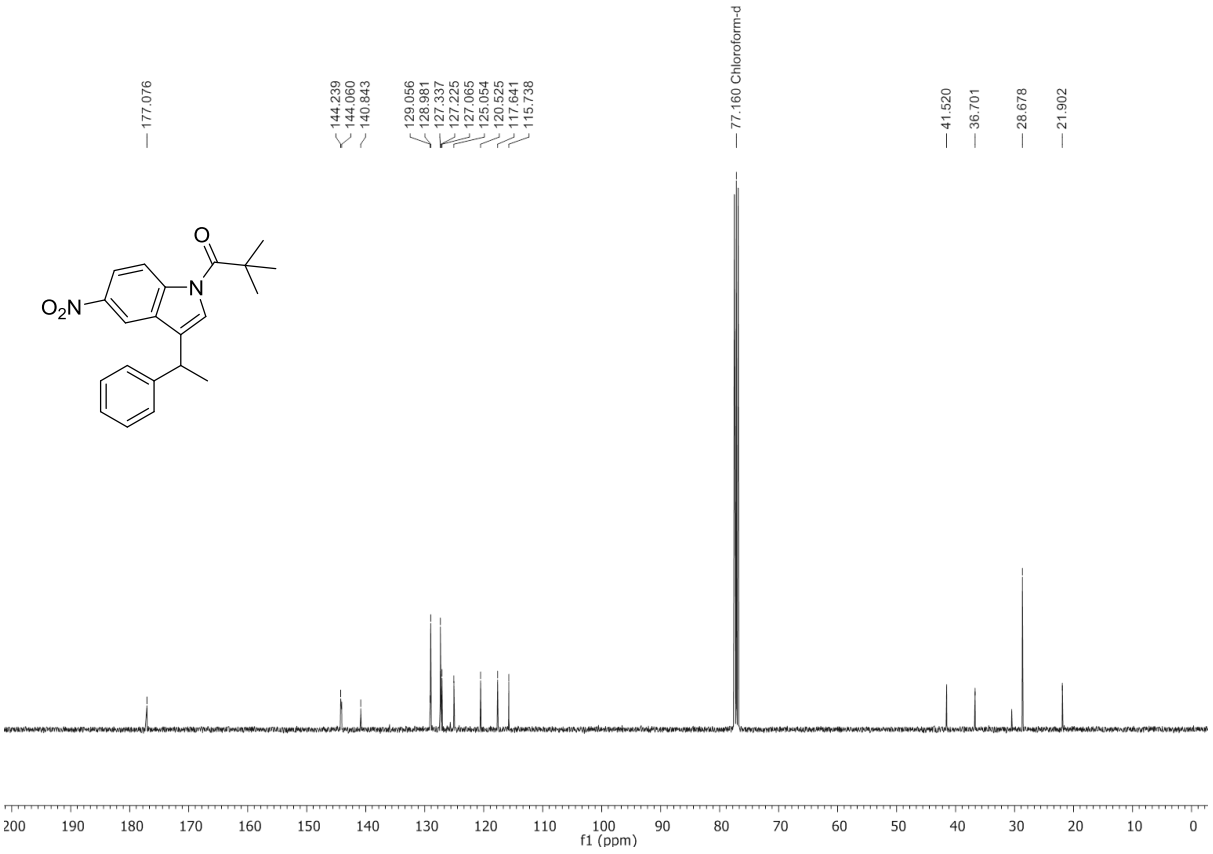
2-Methyl-3-(1-phenylethyl)benzo[b]thiophene **92r**



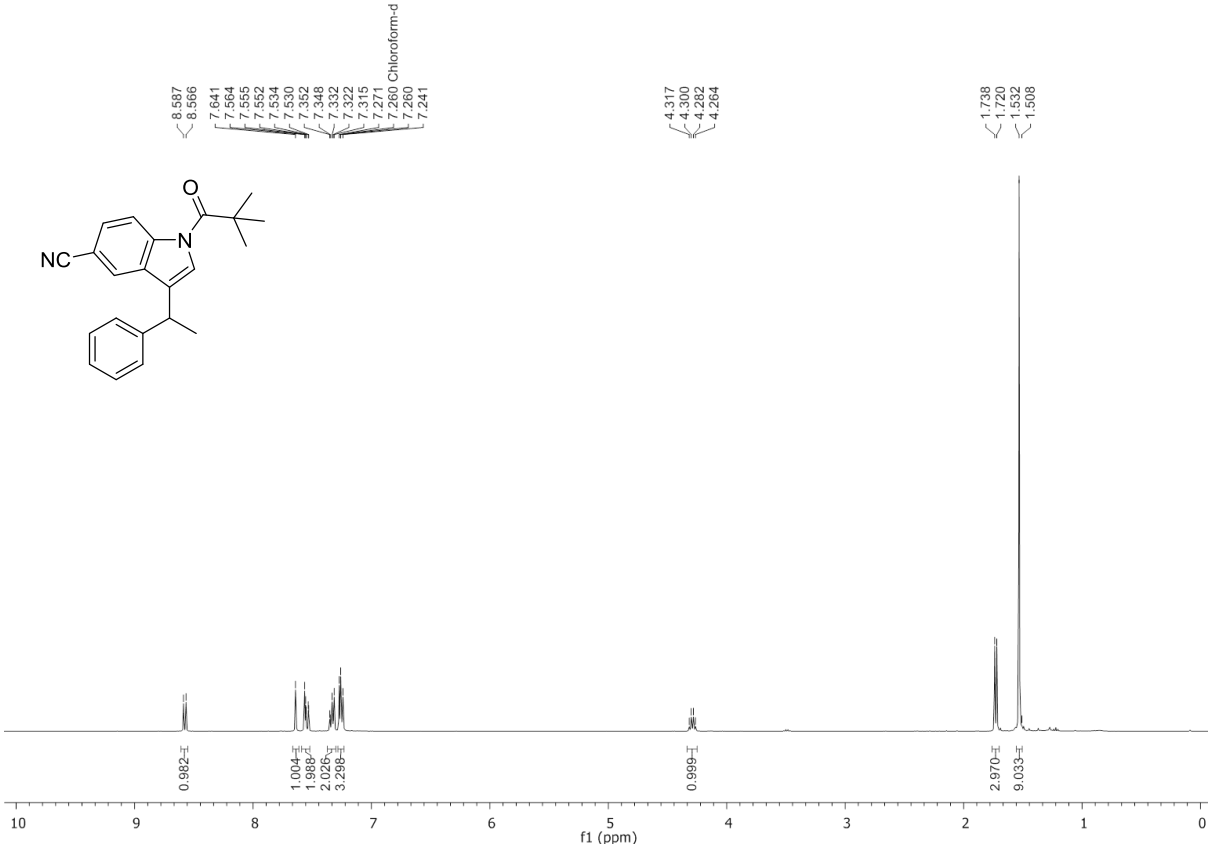


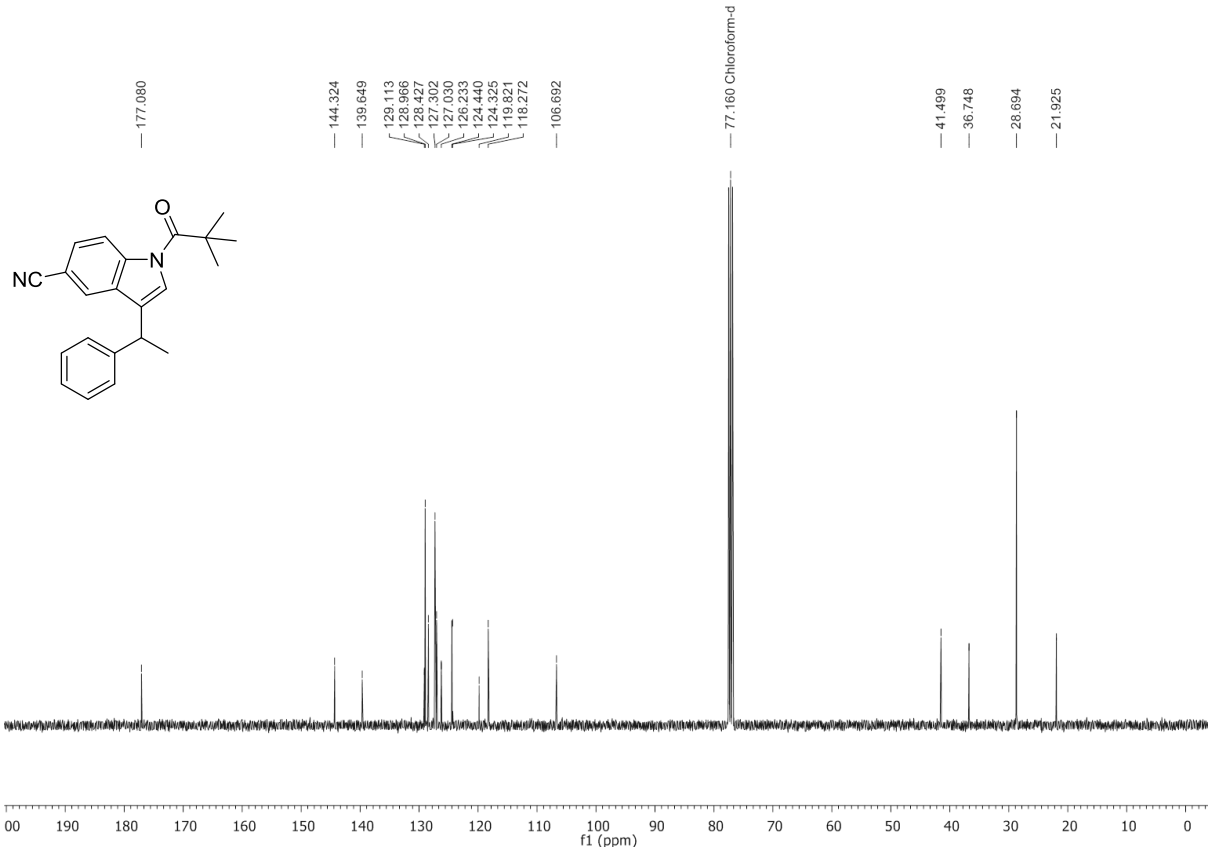
5-Nitro-3-(1-phenylethyl)-1-pivaloylindole **92s**





5-Cyano-3-(1-phenylethyl)-1-pivaloylindole **92t**





S4.6. COMPUTATIONAL SECTION

S4.6.1. Cartesian geometries of Selectfluor II **56** at B3LYP/6-31g (d,p) level of computation.

F	-2.65706800	-0.00032600	-0.00003200
C	-0.81556300	-1.43636900	-0.02176700
C	-0.81573700	0.69938200	1.25445400
C	-0.81567300	0.73717200	-1.23268500
C	0.73673400	-1.43181400	-0.02258500
H	-1.23878200	-1.91871400	0.86076500
H	-1.23991300	-1.89224300	-0.91771800
H	-1.23890100	1.70482200	1.22986300
H	-1.23962500	0.15162100	2.09756700
C	0.73731400	0.69702800	1.25082800
C	0.73732900	0.73610800	-1.22825200
H	-1.23961600	1.74108300	-1.17811300
H	-1.23871100	0.21457000	-2.09207000
H	1.13599700	-1.94203300	0.85542000
H	1.13517400	-1.91388500	-0.91672000
H	1.13585100	1.71280600	1.25144900
H	1.13629100	0.16491300	2.11582300
H	1.13498600	1.75169600	-1.19623700
H	1.13718900	0.23211200	-2.10955200
N	-1.26713300	-0.00037500	-0.00001500
N	1.25506400	-0.00037500	-0.00001500
C	2.77619700	-0.00080700	0.00001400
H	3.12480200	-0.50375500	-0.90268200
H	3.12499700	1.03233800	0.01586600
H	3.12474500	-0.53134000	0.88679500

S4.6.2. Cartesian geometries of 1-fluoroethylbenzene **92a** at B3LYP/6-31g (d) level of computation.

C	-0.67281300	-1.21835100	-0.36036900
C	0.15218300	-0.10031200	-0.19025300
C	-0.42491400	1.12834900	0.14615600
C	-1.80618100	1.23423500	0.31598700
C	-2.62363700	0.11464400	0.15325400
C	-2.05287600	-1.11375900	-0.18643900
H	-0.23533000	-2.17638800	-0.63531600
H	0.21195000	1.99923900	0.25985200
H	-2.24447500	2.19518900	0.57276600
H	-3.69913500	0.19900000	0.28421500
H	-2.68244500	-1.98900900	-0.32377800
C	1.65394500	-0.23606500	-0.33203700
H	1.88764900	-0.88394500	-1.18763500
C	2.33134500	-0.77342100	0.92448200
H	3.41520800	-0.82258200	0.77702700
H	2.11916700	-0.11716400	1.77471100
H	1.96244400	-1.77643600	1.16266900
F	2.21362800	1.01779700	-0.61213300

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Appendix

A.1. BP GEOMETRIES OF STATIONARY POINTS

A.1.1. Cartesian geometries of CP1, CP2, CP4, CP5 and CP6 compounds at BP/TZP level of computation for the chloro benzoic acid case.

***m*-Cl CP1 BP**

C	-0.24100	-0.64400	-0.00100
C	0.93400	0.12500	-0.00200
C	0.86100	1.52800	-0.00200
C	-0.38500	2.15500	0.00000
C	-1.56200	1.40000	0.00200
C	-1.47100	0.00500	0.00000
H	-0.44800	3.24300	0.00100
H	-2.53700	1.88500	0.00400
C	2.23300	-0.60100	0.00000
O	2.34700	-1.82400	0.00100
O	3.30800	0.22900	0.00100
H	4.10400	-0.34900	0.00200
H	1.77300	2.12100	-0.00300
H	-0.17800	-1.73100	-0.00000
C	-2.95200	-0.95500	-0.00000

***o*-Cl CP1 BP**

C	-0.40500	-0.81500	-0.09100
C	0.09400	0.48600	0.13400
C	-0.83800	1.52700	0.31800
C	-2.21000	1.29500	0.25300
C	-2.68000	-0.00100	0.01600
C	-1.77900	-1.05500	-0.14500
H	-2.90700	2.12100	0.38400
H	-3.75000	-0.20000	-0.03900
H	-2.13600	-2.07100	-0.31200
C	1.54700	0.81600	0.12600
O	2.41600	0.20000	-0.48100
O	1.82500	1.92700	0.86200
H	2.78700	2.09700	0.75000
H	-0.46300	2.53300	0.49500
C	0.64700	-2.21800	-0.26100

***p*-Cl CP1 BP**

C	0.37100	-1.23700	-0.00000
C	1.09400	-0.03300	-0.00000
C	0.40400	1.19200	-0.00100
C	-0.99000	1.21500	-0.00100
C	-1.68600	0.00300	0.00000
C	-1.02200	-1.22700	-0.00000
H	-1.53100	2.15900	-0.00100
C	2.57600	-0.10200	-0.00000
O	3.22500	-1.14600	-0.00100
O	3.17200	1.12000	0.00100
H	4.14100	0.95600	0.00200
H	0.95300	2.13100	-0.00100
H	0.91000	-2.18300	-0.00000
C	-3.44600	0.02500	0.00200
H	-1.58600	-2.15800	0.00000

***m*-Cl CP4 BP**

Ag	-0.59000	-0.17400	0.00000
O	-2.64300	-0.86500	0.00000
S	-3.73400	0.27000	0.00000
C	-4.83300	-0.16200	1.37600
H	-5.68600	0.52800	1.34300
H	-5.15500	-1.20500	1.26900
H	-4.26100	-0.01100	2.29700
C	-4.83300	-0.16200	-1.37600
H	-5.15500	-1.20500	-1.26900
H	-5.68600	0.52800	-1.34300
H	-4.26100	-0.01100	-2.29700
C	1.38200	0.42600	0.00000
C	2.43100	-0.52300	0.00000
C	1.75700	1.79000	0.00000
C	3.76500	-0.10600	0.00000
C	3.10000	2.19000	0.00000
H	0.99000	2.56700	0.00000
C	4.12800	1.24000	0.00000
H	3.35800	3.25100	0.00000
H	5.17600	1.53700	0.00000
H	2.22200	-1.59300	0.00000
C	5.05300	-1.34100	0.00000

***o*-Cl CP4 BP**

Ag	-0.26800	-0.04300	0.05200
O	-2.32700	-0.68600	0.13300
S	-3.42700	0.43300	0.04000
C	-4.68900	-0.09500	1.22800
H	-5.54600	0.58400	1.12100
H	-4.97000	-1.13400	1.01900
H	-4.24700	0.00900	2.22500
C	-4.32500	0.06800	-1.49300
H	-4.63600	-0.98400	-1.48800
H	-5.18900	0.74300	-1.53900
H	-3.63800	0.27800	-2.32100
C	1.72700	0.48800	-0.01600
C	2.76600	-0.45500	-0.03200
C	2.15900	1.83700	-0.04700
C	4.12700	-0.13800	-0.07000
C	3.51200	2.19900	-0.08800
H	1.41200	2.63300	-0.03900
C	4.50100	1.20900	-0.09800
H	3.79500	3.25300	-0.11100
H	5.55800	1.47500	-0.12900
H	4.88000	-0.92600	-0.07900
C	2.36700	-2.20900	-0.00500

***p*-Cl CP4 BP**

Ag	-0.75500	-0.40400	0.00500
O	-2.89600	-0.71800	-0.00500
S	-3.76200	0.59400	0.02600
C	-4.96300	0.30900	1.35400
H	-5.65900	1.15800	1.35700
H	-5.48400	-0.64000	1.17500
H	-4.39300	0.28200	2.28900
C	-4.87500	0.43600	-1.39700
H	-5.38600	-0.53300	-1.35200
H	-5.58800	1.27000	-1.35000
H	-4.25300	0.52000	-2.29400
C	1.28900	-0.15500	0.00100
C	2.17800	-1.25400	0.02500
C	1.88600	1.12600	-0.02800
C	3.57300	-1.09800	0.02400
C	3.27800	1.31200	-0.03400
H	1.26400	2.02300	-0.04700
C	4.10500	0.19100	-0.00700
H	3.70800	2.31400	-0.05900
H	1.79100	-2.27400	0.04600
C	5.87000	0.40800	-0.00900
H	4.23300	-1.96500	0.04800

Cl CP6 BP

C	0.00100	0.00000	-2.27900
C	0.00000	-1.21100	-1.57800
C	-0.00100	-1.22000	-0.17800
C	-0.00100	-0.00000	0.50100
C	-0.00100	1.22000	-0.17800
C	0.00000	1.21100	-1.57800
H	0.00200	0.00000	-3.36900
H	0.00000	-2.15900	-2.11600
H	-0.00100	-2.15800	0.37600
H	-0.00100	2.15800	0.37600
H	0.00000	2.15900	-2.11600
C	0.00000	0.00000	2.27200

CO_2 CP5 BP

C	0.00000	0.00000	0.00000
O	0.00000	0.00000	1.17400
O	0.00000	0.00000	-1.17400

CH_3COOAg/DMSO CP2 BP

O	3.01000	1.30500	0.00000
O	2.36300	-0.86200	0.00000
O	-1.59900	0.70600	0.00000
S	-2.69800	-0.42600	0.00000
C	-3.79100	0.01500	-1.37600
H	-4.64400	-0.67500	-1.34900
H	-4.11300	1.05800	-1.26600
H	-3.21600	-0.13300	-2.29700

C	-3.79100	0.01500	1.37600
H	-4.11300	1.05800	1.26600
H	-4.64400	-0.67500	1.34900
H	-3.21600	-0.13300	2.29700
C	3.26800	0.07600	0.00000
Ag	0.42000	-0.00400	0.00000
C	4.70500	-0.42000	0.00000
H	4.88000	-1.04800	0.88500
H	4.88000	-1.04800	-0.88500
H	5.40700	0.42000	0.00000

CH_3COOH CP7 BP

C	0.11500	0.09300	-0.00000
O	1.17200	0.71600	0.00000
O	-1.09300	0.72300	-0.00000
H	-0.90500	1.68900	0.00100
C	-0.02700	-1.40100	0.00000
H	-0.59500	-1.71700	0.88500
H	-0.59500	-1.71700	-0.88500
H	0.96100	-1.86800	-0.00000

A.1.2. Cartesian geometries of CP3 compounds at BP/TZP level of computation.

***m*-Br CP3 BP**

O	0.49700	-1.21500	-0.13700
O	-0.30300	0.89900	0.00600
Ag	-2.19500	-0.04500	-0.15200
O	-4.21400	-0.70800	-0.32700
S	-4.50800	-2.24700	-0.13800
C	-5.54400	-2.66600	-1.56500
H	-5.89000	-3.69800	-1.42700
H	-6.38400	-1.96400	-1.61800
H	-4.90500	-2.59700	-2.45200
C	-5.78200	-2.29500	1.15100
H	-6.59900	-1.61900	0.87400
H	-6.12800	-3.33400	1.23100
H	-5.30100	-1.98400	2.08400
C	2.05500	0.59800	0.06500
C	2.27300	1.98000	0.17800
C	3.15100	-0.28000	0.03600
C	3.57500	2.48100	0.26200
H	1.41900	2.65400	0.20000
C	4.43800	0.24300	0.12200
C	4.67400	1.61500	0.23400
H	3.74400	3.55400	0.35000
H	5.69000	2.00200	0.29900
C	0.65900	0.02400	-0.03000
H	2.97600	-1.35100	-0.05200
Br	5.95000	-0.96900	0.08200

***o*-Br CP3 BP**

O	0.73300	-0.62100	-0.89900
O	0.25900	0.95900	0.65100
Ag	-1.70300	0.15600	0.43800
O	-3.66900	-0.66500	0.29200
S	-4.82100	0.30800	-0.17300
C	-6.31000	-0.45400	0.51700
H	-7.17300	0.09800	0.12100
H	-6.34100	-1.51100	0.22800
H	-6.25000	-0.33400	1.60400
C	-5.09100	-0.09500	-1.92200
H	-5.25000	-1.17400	-2.02600
H	-5.96500	0.47800	-2.26000
H	-4.19600	0.23200	-2.46400
C	2.47900	0.85900	-0.18000
C	2.67200	2.25100	-0.27100
C	3.62600	0.04800	-0.17500
C	3.94800	2.80600	-0.38600
H	1.79200	2.89400	-0.26000
C	4.91100	0.58700	-0.26800
C	5.07100	1.97100	-0.38600
H	4.06700	3.88600	-0.47100
H	5.77900	-0.07100	-0.24600
H	6.07400	2.38800	-0.47000
C	1.06100	0.32800	-0.15300
Br	3.51100	-1.87400	0.03700

***p*-Br CP3 BP**

O	0.05000	-1.88300	0.00000
O	-0.32200	0.35100	0.00000
Ag	-2.36700	-0.20400	0.00000
O	-4.48300	-0.46100	0.00000
S	-5.04000	-1.93700	0.00000
C	-6.21900	-1.95800	-1.37500
H	-6.74300	-2.92200	-1.34300
H	-6.91500	-1.11700	-1.26600
H	-5.63200	-1.87600	-2.29700
C	-6.21900	-1.95800	1.37500
H	-6.91500	-1.11700	1.26600
H	-6.74300	-2.92200	1.34300
H	-5.63200	-1.87600	2.29700
C	1.93200	-0.40200	0.00000
C	2.41200	0.91800	0.00000
C	2.85000	-1.46500	0.00000
C	3.78400	1.17900	0.00000
H	1.70500	1.74500	0.00000
C	4.22500	-1.22300	0.00000
C	4.67000	0.10100	0.00000
H	4.15500	2.20300	0.00000

C	0.45200	-0.69500	0.00000
H	2.47800	-2.48800	0.00000
H	4.93500	-2.04800	0.00000
Br	6.56900	0.45000	0.00000

***m*-CF_3 CP3 BP**

O	1.35900	-1.58200	-0.00800
O	0.74700	0.59800	-0.05400
Ag	-1.22400	-0.18600	-0.06900
O	-3.29600	-0.69200	-0.10400
S	-3.69300	-2.19600	0.15900
C	-4.80200	-2.60100	-1.21600
H	-5.22800	-3.59100	-1.01200
H	-5.58200	-1.83300	-1.28600
H	-4.18600	-2.63200	-2.12200
C	-4.92300	-2.09700	1.48600
H	-5.69800	-1.37500	1.20200
H	-5.34100	-3.10300	1.62300
H	-4.39000	-1.78100	2.39000
C	3.07000	0.09600	-0.01800
C	3.40900	1.46000	-0.03200
C	4.08800	-0.86400	0.00300
C	4.74800	1.85500	-0.02500
H	2.61500	2.20400	-0.04900
C	5.42900	-0.46100	0.01000
C	5.76600	0.89700	-0.00500
H	5.00500	2.91400	-0.03600
H	6.81000	1.20500	-0.00000
C	1.62800	-0.35700	-0.02600
H	3.81700	-1.92000	0.01400
C	6.49700	-1.51900	0.03300
F	7.75800	-1.00500	0.02200
F	6.40600	-2.32200	1.14500
F	6.40700	-2.36900	-1.04400

***o*-CF_3 CP3 BP**

O	1.42200	-1.32600	-0.84200
O	0.94400	0.28900	0.67500
Ag	-1.06900	-0.28900	0.32500
O	-3.15800	-0.62800	0.04700
S	-3.63200	-2.12800	-0.07800
C	-4.88000	-2.07500	-1.38900
H	-5.34400	-3.06800	-1.43800
H	-5.61700	-1.29700	-1.15500
H	-4.35100	-1.85900	-2.32400
C	-4.73400	-2.37200	1.34200
H	-5.47500	-1.56500	1.36500
H	-5.21000	-3.35300	1.22200
H	-4.10400	-2.36500	2.23800
C	3.19800	0.06400	-0.02000
C	3.43500	1.44400	-0.11300
C	4.31200	-0.80500	0.04800
C	4.73200	1.95700	-0.17300
H	2.57800	2.11500	-0.14900
C	5.61200	-0.28500	0.00500
C	5.82500	1.09000	-0.11700
H	4.88600	3.03300	-0.26000
H	6.46400	-0.95800	0.07600
H	6.84300	1.47700	-0.15700
C	1.75300	-0.39600	-0.07400
C	4.16000	-2.30100	0.19700
F	5.30600	-2.88700	0.66700
F	3.16900	-2.65200	1.07000
F	3.88300	-2.93400	-0.99000

***p*-CF_3 CP3 BP**

O	0.80200	-1.46200	0.01600
O	0.76000	0.80100	0.06400
Ag	-1.34600	0.54200	0.05400
O	-3.48000	0.58000	0.04100
S	-4.23000	-0.80800	0.05300
C	-5.33500	-0.72700	-1.38100
H	-5.97800	-1.61600	-1.34900
H	-5.92200	0.19700	-1.33200
H	-4.70000	-0.75100	-2.27400
C	-5.46500	-0.62400	1.36600

H	-6.04800	0.28800	1.19100
H	-6.10100	-1.51900	1.34400
H	-4.91600	-0.57500	2.31300
C	2.88200	-0.27300	0.02500
C	3.55100	0.96000	0.05800
C	3.63100	-1.46100	-0.02600
C	4.94600	1.01100	0.03800
H	2.97300	1.88200	0.09700
C	5.02300	-1.41900	-0.04900
C	5.67900	-0.17900	-0.01800
H	5.45800	1.97200	0.06300
C	1.37100	-0.34600	0.03500
H	3.10700	-2.41500	-0.05200
H	5.59600	-2.34500	-0.09200
C	7.18200	-0.15700	-0.04100
F	7.69900	1.10200	-0.08900
F	7.69200	-0.83700	-1.12100
F	7.72400	-0.76400	1.06700

***m*-CH_3 CP3 BP**

O	1.18000	-1.36300	0.00000
O	0.70500	0.84600	0.00000
Ag	-1.27700	0.06300	0.00000
O	-3.27000	-0.69800	0.00000
S	-4.45500	0.34300	0.00000
C	-5.50700	-0.19300	1.37500
H	-6.41700	0.42100	1.34900
H	-5.73700	-1.25900	1.26100
H	-4.94600	0.00100	2.29500
C	-5.50700	-0.19300	-1.37500
H	-5.73700	-1.25900	-1.26100
H	-6.41700	0.42100	-1.34900
H	-4.94600	0.00100	-2.29500
C	3.00000	0.20000	0.00000
C	3.42800	1.53900	0.00000
C	3.95300	-0.83000	0.00000
C	4.79400	1.82700	0.00000
H	2.68900	2.33900	0.00000
C	5.32900	-0.55500	0.00000
C	5.73400	0.79000	0.00000
H	5.13200	2.86400	0.00000
H	6.80000	1.02800	0.00000
C	1.53400	-0.15700	0.00000
H	3.60000	-1.86200	0.00000
C	6.33900	-1.67900	0.00000
H	6.21400	-2.32300	0.88300
H	6.21400	-2.32300	-0.88300
H	7.36500	-1.29300	0.00000

***o*-CH_3 CP3 BP**

O	1.36500	-1.41900	0.00000
O	0.88300	0.78100	0.00000
Ag	-1.08400	-0.05100	0.00000
O	-3.15900	-0.58000	0.00000
S	-3.50500	-2.11900	0.00000
C	-4.66900	-2.31200	-1.37600
H	-5.04500	-3.34300	-1.34300
H	-5.48200	-1.58300	-1.26600
H	-4.10200	-2.14500	-2.29800
C	-4.66900	-2.31200	1.37600
H	-5.48200	-1.58300	1.26600
H	-5.04500	-3.34300	1.34300
H	-4.10200	-2.14500	2.29800
C	3.19000	0.16500	0.00000
C	3.51500	1.53700	0.00000
C	4.23700	-0.79800	0.00000
C	4.83700	1.97800	0.00000
H	2.69800	2.25600	0.00000
C	5.56300	-0.32600	0.00000
C	5.87000	1.03700	0.00000
H	5.05900	3.04600	0.00000
H	6.37500	-1.05600	0.00000
H	6.91200	1.35900	0.00000
C	1.72600	-0.21600	0.00000
C	4.02400	-2.29300	0.00000
H	3.44900	-2.61900	0.87600

H	3.44900	-2.61900	-0.87600
H	4.99400	-2.80700	0.00000

p-CH_3 CP3 BP

O	0.69500	-1.26800	0.00000
O	0.75400	0.99200	0.00000
Ag	-1.35900	0.73800	0.00000
O	-3.49700	0.67800	0.00000
S	-4.14400	-0.76100	0.00000
C	-5.32300	-0.71800	-1.37600
H	-5.89700	-1.65300	-1.34300
H	-5.97300	0.15800	-1.26700
H	-4.73300	-0.67000	-2.29800
C	-5.32300	-0.71800	1.37600
H	-5.97300	0.15800	1.26700
H	-5.89700	-1.65300	1.34300
H	-4.73300	-0.67000	2.29800
C	2.82900	-0.18000	0.00000
C	3.56600	1.01400	0.00000
C	3.52600	-1.40200	0.00000
C	4.96300	0.98700	0.00000
H	3.03700	1.96700	0.00000
C	4.92000	-1.42400	0.00000
C	5.66600	-0.23000	0.00000
H	5.51900	1.92600	0.00000
C	1.32300	-0.18000	0.00000
H	2.95900	-2.33200	0.00000
H	5.44300	-2.38300	0.00000
C	7.17500	-0.26200	0.00000
H	7.59600	0.75100	0.00000
H	7.55800	-0.79400	0.88300
H	7.55800	-0.79400	-0.88300

***o*-Cl+*m*-Me CP3 BP**

O	0.74200	-0.03100	-1.40300
O	0.71000	-0.27300	0.84900
Ag	-1.38600	0.01200	0.62800
O	-3.48000	0.42100	0.61600
S	-4.34000	-0.23300	-0.53500
C	-4.73900	1.14300	-1.64900
H	-5.45400	0.76600	-2.39100
H	-5.16200	1.97000	-1.06600
H	-3.80600	1.43700	-2.14300
C	-5.96700	-0.44400	0.23100
H	-6.28800	0.51100	0.66400
H	-6.65600	-0.78400	-0.55200
H	-5.85400	-1.21700	0.99900
C	2.81600	-0.32800	-0.24700
C	3.63700	0.80200	-0.15600
C	3.41900	-1.60600	-0.32400
C	5.03000	0.71300	-0.14200
C	4.81800	-1.69400	-0.30700
C	5.61900	-0.55100	-0.21800
H	5.63400	1.61600	-0.07100
H	5.28600	-2.67800	-0.36600
H	6.70400	-0.64100	-0.20600
C	1.30400	-0.19200	-0.29900
C	2.56900	-2.84900	-0.43000
H	1.87700	-2.93200	0.42100
H	1.95500	-2.83300	-1.34300
H	3.19600	-3.74800	-0.45600
Cl	2.90000	2.41200	-0.05700

***o*-NO_2+*m*-Me CP3 BP**

O	1.09100	-1.42700	-0.75800
O	1.09800	0.02700	0.98000
Ag	-0.87300	-0.69500	1.31500
O	-2.80900	-1.36500	1.91200
S	-3.95100	-1.39800	0.82400
C	-5.36600	-0.64000	1.66300
H	-6.23900	-0.75800	1.00900
H	-5.51800	-1.13500	2.63000
H	-5.12800	0.42200	1.78900
C	-4.51500	-3.12100	0.83300
H	-4.73400	-3.42100	1.86400
H	-5.40900	-3.17800	0.19900

H	-3.70700	-3.72300	0.40200
C	3.05300	-0.12600	-0.35500
C	3.19000	0.97100	-1.23600
C	4.22600	-0.74300	0.12300
C	4.47600	1.40000	-1.59300
C	5.50700	-0.30800	-0.24200
C	5.62700	0.77200	-1.10400
H	4.57500	2.24900	-2.27100
H	6.37800	-0.82100	0.15800
H	6.61400	1.12800	-1.39800
C	1.64400	-0.58900	-0.01600
N	4.14400	-1.88200	1.03900
O	5.20400	-2.43200	1.40400
O	3.01900	-2.25900	1.41900
C	1.97500	1.67600	-1.78900
H	1.31300	0.97300	-2.31300
H	1.38500	2.13600	-0.98400
H	2.26900	2.46200	-2.49200

***m*-CN CP3 BP**

O	1.04300	-1.23200	-0.07000
O	0.50000	0.96200	0.01000
Ag	-1.45900	0.11200	0.04700
O	-3.39900	-0.76400	0.14100
S	-4.65500	0.16400	-0.07700
C	-5.75800	-0.26600	1.29600
H	-6.70700	0.26000	1.13000
H	-5.89800	-1.35300	1.32000
H	-5.27900	0.09800	2.21200
C	-5.56600	-0.64100	-1.42100
H	-5.71400	-1.69900	-1.17300
H	-6.52300	-0.11500	-1.53100
H	-4.96300	-0.52200	-2.32800
C	2.81000	0.37900	-0.01600
C	3.21000	1.72400	0.04200
C	3.78100	-0.62600	-0.05300
C	4.56600	2.06300	0.06400
H	2.44800	2.50200	0.07100
C	5.14300	-0.28300	-0.03000
C	5.54100	1.06700	0.02900
H	4.86700	3.10900	0.11000
H	6.59900	1.32100	0.04800
C	1.35100	-0.01700	-0.03000
C	6.12900	-1.31600	-0.06700
N	6.93100	-2.16300	-0.09700
H	3.47100	-1.66800	-0.09800

***o*-CN CP3 BP**

O	1.42700	-1.35600	-0.06600
O	0.74500	0.80100	0.03500
Ag	-1.20500	-0.03800	-0.03600
O	-3.25400	-0.61900	-0.12300
S	-3.60200	-2.14200	0.09900
C	-4.65600	-2.55900	-1.31400
H	-5.04400	-3.57300	-1.14600
H	-5.46700	-1.82500	-1.38700
H	-4.01600	-2.54200	-2.20300
C	-4.87300	-2.11700	1.39100
H	-5.66700	-1.41900	1.09900
H	-5.25400	-3.14100	1.49500
H	-4.38000	-1.80100	2.31600
C	3.08000	0.36900	0.02800
C	3.35600	1.74000	0.09000
C	4.16900	-0.53600	-0.00300
C	4.66900	2.21400	0.11900
H	2.51700	2.43200	0.11500
C	5.49400	-0.05500	0.02700
C	5.74000	1.31500	0.08800
H	4.85700	3.28600	0.16700
H	6.31900	-0.76500	0.00200
H	6.76700	1.67700	0.11000
C	1.65300	-0.12500	-0.00500
C	4.01400	-1.95900	-0.06700
N	4.07700	-3.12400	-0.11800

***p*-CN CP3 BP**

O	0.91000	-1.72600	0.00000
O	0.51800	0.50400	0.00000
Ag	-1.51400	-0.12500	0.00000
O	-3.60900	-0.54300	0.00000
S	-4.04000	-2.06100	0.00000
C	-5.21200	-2.18600	-1.37600
H	-5.64900	-3.19300	-1.34300
H	-5.98000	-1.41100	-1.26700
H	-4.63500	-2.05500	-2.29800
C	-5.21200	-2.18600	1.37600
H	-5.98000	-1.41100	1.26700
H	-5.64900	-3.19300	1.34300
H	-4.63500	-2.05500	2.29800
C	2.78100	-0.23200	0.00000
C	3.25100	1.09100	0.00000
C	3.70000	-1.29500	0.00000
C	4.61700	1.35500	0.00000
H	2.53700	1.91100	0.00000
C	5.06800	-1.04800	0.00000
C	5.52900	0.28300	0.00000
H	4.98400	2.38000	0.00000
C	1.29900	-0.53400	0.00000
H	5.78200	-1.87000	0.00000
H	3.32500	-2.31700	0.00000
C	6.93400	0.54700	0.00000
N	8.08000	0.76200	0.00000

***m*-CHO CP3 BP**

O	1.05200	-1.34000	0.00000
O	0.44100	0.83700	0.00000
Ag	-1.51100	-0.02300	0.00000
O	-3.55300	-0.65000	0.00000
S	-3.83700	-2.20100	0.00000
C	-4.99400	-2.43700	-1.37500
H	-5.33600	-3.47900	-1.34000
H	-5.82900	-1.73500	-1.26700
H	-4.43200	-2.25400	-2.29800
C	-4.99400	-2.43700	1.37500
H	-5.82900	-1.73500	1.26700
H	-5.33600	-3.47900	1.34000
H	-4.43200	-2.25400	2.29800
C	2.76700	0.32500	0.00000
C	3.12400	1.68300	0.00000
C	3.77900	-0.64200	0.00000
C	4.47100	2.07000	0.00000
H	2.33700	2.43500	0.00000
C	5.12800	-0.26000	0.00000
C	5.47500	1.10500	0.00000
H	4.73100	3.12900	0.00000
C	1.32300	-0.11600	0.00000
H	3.50700	-1.69800	0.00000
H	6.52800	1.38800	0.00000
C	6.15300	-1.31800	0.00000
H	5.75400	-2.35500	0.00000
O	7.37100	-1.12100	0.00000

***o*-CHO CP3 BP**

O	1.43800	-1.45400	0.13100
O	0.68900	0.63700	-0.30800
Ag	-1.19500	-0.33800	-0.44800
O	-3.16700	-1.12500	-0.67000
S	-3.70400	-1.99000	0.53700
C	-4.90500	-3.09500	-0.24600
H	-5.41000	-3.64900	0.55600
H	-5.61600	-2.50000	-0.83200
H	-4.33600	-3.78300	-0.88100
C	-4.86000	-0.90100	1.41400
H	-5.58000	-0.48700	0.69800
H	-5.35800	-1.50600	2.18300
H	-4.26000	-0.11300	1.88300
C	2.99900	0.36800	0.18100
C	3.11300	1.65100	0.73500
C	4.36500	2.19200	1.03900
H	2.20500	2.21400	0.94600
C	5.43400	0.19600	0.20300

C	5.53100	1.46300	0.77600
H	4.43000	3.18600	1.48300
C	1.61900	-0.22100	-0.01700
H	6.50800	1.88600	1.00700
C	4.18100	-0.36500	-0.09900
C	4.15000	-1.67500	-0.79200
H	3.19800	-1.94700	-1.28200
O	5.12200	-2.43400	-0.86100
H	6.33000	-0.37800	-0.03700

***p*-CHO CP3 BP**

O	0.85900	-1.83300	0.00800
O	0.47400	0.39900	-0.00100
Ag	-1.56700	-0.18900	-0.00100
O	-3.68000	-0.49100	-0.00100
S	-4.21000	-1.97700	-0.00500
C	-5.39300	-2.01400	-1.37800
H	-5.89100	-2.99300	-1.35400
H	-6.11100	-1.19400	-1.25700
H	-4.81200	-1.90800	-2.30000
C	-5.38400	-2.02800	1.37400
H	-6.09800	-1.20200	1.27100
H	-5.88700	-3.00300	1.34000
H	-4.79600	-1.93800	2.29400
C	2.73600	-0.34100	0.00300
C	3.20600	0.98700	-0.00300
C	3.65300	-1.40400	0.00900
C	4.57200	1.24800	-0.00500
H	2.48600	1.80400	-0.00700
C	5.02100	-1.14600	0.00800
C	5.49000	0.18100	0.00000
H	4.94500	2.27200	-0.01100
C	1.25200	-0.64200	0.00400
H	5.73800	-1.96800	0.01200
H	3.27700	-2.42600	0.01400
C	6.94500	0.41200	-0.00400
H	7.56500	-0.51100	0.00400
O	7.48500	1.52100	-0.01500

***m*-Cl CP3 BP**

O	1.63000	-1.69300	0.31300
O	1.10100	0.46300	-0.13100
Ag	-0.89100	-0.22200	0.10700
O	-2.96600	-0.65000	0.36400
S	-3.49500	-2.02300	-0.20700
C	-4.69400	-1.54800	-1.48100
H	-5.18700	-2.46700	-1.82500
H	-5.41400	-0.84000	-1.05400
H	-4.12400	-1.09700	-2.30100
C	-4.65500	-2.59100	1.06400
H	-5.36800	-1.78700	1.28500
H	-5.16000	-3.48200	0.67100
H	-4.05800	-2.85200	1.94500
C	3.40500	-0.12800	-0.07900
C	3.79700	1.18900	-0.36400
C	4.38100	-1.12100	0.09800
C	5.15200	1.51100	-0.47100
H	3.03400	1.95400	-0.50000
C	5.72600	-0.77800	-0.01300
C	6.13200	0.52800	-0.29500
H	5.45600	2.53300	-0.69200
H	7.19000	0.77100	-0.37600
C	1.94600	-0.50900	0.04900
Cl	6.95600	-2.03100	0.21400
H	4.07700	-2.14300	0.32000

***o*-Cl CP3 BP**

O	1.37200	-0.35300	-1.28100
O	1.12300	0.06000	0.93200
Ag	-0.92700	0.28800	0.43400
O	-3.02200	0.61200	0.18700
S	-3.70400	-0.03200	-1.08200
C	-4.93400	1.20300	-1.57500
H	-5.53900	0.75900	-2.37600
H	-5.54700	1.46700	-0.70600
H	-4.38100	2.06900	-1.95400

C	-4.83000	-1.28400	-0.40600
H	-5.46000	-0.82400	0.36400
H	-5.43000	-1.66800	-1.24200
H	-4.20600	-2.08300	0.00900
C	3.31800	-0.29900	0.12800
C	3.91300	0.66800	0.96000
C	4.16200	-1.26300	-0.45100
C	5.29000	0.69600	1.18100
H	3.26600	1.41200	1.42500
C	5.54000	-1.26100	-0.22100
C	6.10600	-0.27300	0.58800
H	5.72300	1.46700	1.81800
H	6.16100	-2.03300	-0.67300
H	7.18300	-0.27000	0.75700
C	1.82800	-0.21100	-0.12500
Cl	3.52100	-2.57100	-1.45400

***p*-Cl CP3 BP**

O	1.63700	-1.67300	0.45000
O	1.13300	0.45400	-0.13800
Ag	-0.86800	-0.21500	0.04500
O	-2.95800	-0.60800	0.21900
S	-3.47300	-2.03400	-0.21500
C	-4.77300	-1.68300	-1.42800
H	-5.25700	-2.63700	-1.67300
H	-5.48500	-0.96900	-0.99900
H	-4.27700	-1.27300	-2.31500
C	-4.52200	-2.55400	1.16800
H	-5.24600	-1.76000	1.38900
H	-5.02400	-3.48300	0.86900
H	-3.85800	-2.74000	2.01900
C	3.43000	-0.13200	0.06100
C	3.83500	1.16700	-0.28600
C	4.40800	-1.09800	0.34700
C	5.18900	1.50100	-0.34700
H	3.08200	1.92100	-0.50900
C	5.76500	-0.78100	0.29200
C	6.13800	0.51900	-0.05500
H	5.50400	2.50800	-0.61600
C	1.97000	-0.50500	0.13700
H	4.09300	-2.10600	0.61600
H	6.52400	-1.53000	0.51500
Cl	7.85300	0.93300	-0.12600

***m*-Et CP3 BP**

O	1.32400	-1.53200	0.01000
O	0.72800	0.64800	-0.09700
Ag	-1.23100	-0.16500	-0.11000
O	-3.29000	-0.72000	-0.17200
S	-3.66300	-2.17400	0.31200
C	-4.83600	-2.75400	-0.94100
H	-5.24300	-3.71100	-0.59100
H	-5.62500	-2.00400	-1.06900
H	-4.26500	-2.90000	-1.86500
C	-4.82600	-1.90400	1.67600
H	-5.62700	-1.23300	1.34200
H	-5.21800	-2.88600	1.97200
H	-4.25200	-1.46500	2.50000
C	3.05200	0.13500	-0.02500
C	3.39600	1.49800	-0.05900
C	4.06800	-0.82900	0.01800
C	4.73900	1.87100	-0.05100
H	2.60800	2.25000	-0.09300
C	5.42700	-0.47100	0.02700
C	5.74600	0.89600	-0.00900
H	5.01100	2.92700	-0.07800
H	6.79000	1.21100	-0.00500
C	1.61000	-0.30900	-0.03700
H	3.78400	-1.88300	0.04400
C	6.48300	-1.56400	0.07500
H	6.32000	-2.15600	0.99100
H	6.29100	-2.26200	-0.75500
C	7.93900	-1.10000	0.02500
H	8.61200	-1.96600	0.05700
H	8.15500	-0.54100	-0.89800
H	8.18900	-0.45000	0.87600

***o*-Et CP3 BP**

O	1.38300	-1.31800	0.62900
O	0.91200	0.64000	-0.39200
Ag	-1.07600	-0.07200	-0.12200
O	-3.14900	-0.55300	0.09700
S	-3.54200	-2.07800	0.02500
C	-4.83000	-2.14600	-1.24800
H	-5.22600	-3.17000	-1.25800
H	-5.61200	-1.41400	-1.01200
H	-4.34400	-1.92000	-2.20400
C	-4.58500	-2.33400	1.48500
H	-5.37400	-1.57200	1.50200
H	-5.00500	-3.34600	1.41200
H	-3.93100	-2.25800	2.36000
C	3.19800	0.17300	0.08400
C	3.49000	1.54800	0.14300
C	4.25800	-0.77400	0.03100
C	4.80500	2.01400	0.17600
H	2.65800	2.25100	0.17000
C	5.57300	-0.27700	0.04600
C	5.85200	1.09100	0.12900
H	5.00800	3.08300	0.23600
H	6.40600	-0.97800	-0.00800
H	6.88800	1.43100	0.14900
C	1.74000	-0.23000	0.11600
C	4.00600	-2.27200	-0.06800
H	3.50500	-2.60000	0.85400
H	3.26000	-2.44600	-0.85800
C	5.23500	-3.14800	-0.32800
H	5.75200	-2.86600	-1.25700
H	5.96400	-3.09100	0.49200
H	4.92600	-4.19800	-0.42300

***p*-Et CP3 BP**

O	0.80200	-1.41800	-0.08900
O	0.74800	0.83700	0.09000
Ag	-1.35200	0.58900	0.01200
O	-3.47800	0.71100	-0.10100
S	-4.30800	-0.62000	0.06200
C	-5.40700	-0.62600	-1.37900
H	-6.10600	-1.46400	-1.25600
H	-5.93500	0.33400	-1.43300
H	-4.77600	-0.78900	-2.25900
C	-5.53100	-0.22200	1.33900
H	-6.05700	0.69900	1.06100
H	-6.22000	-1.07400	1.40800
H	-4.98100	-0.10400	2.27900
C	2.87600	-0.21900	-0.00500
C	3.54200	1.01200	0.09600
C	3.64500	-1.39100	-0.11600
C	4.93900	1.07100	0.08700
H	2.95800	1.92800	0.18200
C	5.03600	-1.32800	-0.12600
C	5.71300	-0.09600	-0.02600
H	5.42700	2.04200	0.16700
C	1.37200	-0.30200	-0.00300
H	3.13600	-2.35100	-0.19600
H	5.61700	-2.24900	-0.21300
C	7.23200	-0.07900	-0.04300
H	7.58900	-0.71900	0.78000
H	7.56700	-0.58400	-0.96300
C	7.89600	1.29500	0.05600
H	7.60400	1.94800	-0.78000
H	7.63200	1.80800	0.99200
H	8.98900	1.18800	0.03000

***m*-F CP3 BP**

O	1.19500	-1.42600	-0.04300
O	0.72400	0.77800	0.16700
Ag	-1.27700	0.05900	0.22000
O	-3.30500	-0.60200	0.30500
S	-4.41000	0.37400	-0.25600
C	-5.77400	0.19600	0.92400
H	-6.63200	0.74600	0.51700
H	-6.00300	-0.86800	1.05100

H	-5.44200	0.65300	1.86300
C	-5.13900	-0.52500	-1.65300
H	-5.43600	-1.52700	-1.32300
H	-6.00200	0.05700	-2.00200
H	-4.37400	-0.56900	-2.43600
C	3.01100	0.13800	-0.01200
C	3.44800	1.46800	0.10700
C	3.95300	-0.89100	-0.17900
C	4.81300	1.76800	0.06200
H	2.71300	2.26000	0.23600
C	5.29700	-0.55500	-0.22100
C	5.76000	0.75100	-0.10500
H	5.14900	2.80000	0.15700
H	6.82800	0.95900	-0.14400
C	1.54400	-0.22200	0.03800
H	3.63000	-1.92700	-0.27300
F	6.22000	-1.56500	-0.38700

***o*-F CP3 BP**

O	1.28300	-1.40800	0.00000
O	0.86100	0.80900	0.00000
Ag	-1.13900	0.05800	0.00000
O	-3.15400	-0.64800	0.00000
S	-4.30800	0.42700	0.00000
C	-5.37700	-0.07400	1.37500
H	-6.27000	0.56400	1.34500
H	-5.63600	-1.13400	1.26400
H	-4.81400	0.10800	2.29700
C	-5.37700	-0.07400	-1.37500
H	-5.63600	-1.13400	-1.26400
H	-6.27000	0.56400	-1.34500
H	-4.81400	0.10800	-2.29700
C	3.13500	0.13200	0.00000
C	3.54700	1.48100	0.00000
C	4.15800	-0.83100	0.00000
C	4.89400	1.84000	0.00000
H	2.77100	2.24400	0.00000
C	5.50900	-0.50100	0.00000
C	5.88000	0.84500	0.00000
H	5.17800	2.89200	0.00000
H	6.25000	-1.30100	0.00000
H	6.93700	1.11200	0.00000
C	1.66500	-0.21300	0.00000
F	3.86000	-2.16800	0.00000

***p*-F CP3 BP**

O	1.18400	-1.72300	0.09700
O	0.73500	0.48300	-0.13200
Ag	-1.28000	-0.18500	-0.15800
O	-3.37900	-0.56500	-0.24100
S	-3.87500	-2.00700	0.16200
C	-4.93800	-2.50800	-1.21700
H	-5.41300	-3.45600	-0.93500
H	-5.68200	-1.72400	-1.40300
H	-4.28400	-2.65600	-2.08400
C	-5.16200	-1.69900	1.40100
H	-5.88300	-0.97800	0.99900
H	-5.63700	-2.66200	1.62500
H	-4.65800	-1.30900	2.29300
C	3.01400	-0.17700	0.03200
C	3.44900	1.15500	-0.07900
C	3.96700	-1.20000	0.17700
C	4.81100	1.46700	-0.04800
H	2.71400	1.95000	-0.19100
C	5.33200	-0.90900	0.21100
C	5.71700	0.42300	0.09600
H	5.16600	2.49300	-0.13300
C	1.54800	-0.52500	0.00000
H	3.62600	-2.23100	0.26400
H	6.08300	-1.68900	0.32200
F	7.05800	0.72100	0.12800

***m*-NH_2 CP3 BP**

N	6.27400	-1.28600	1.08400
C	-5.00700	-1.96600	-1.69700
C	-4.88500	-2.20000	1.04000

C	3.03700	0.18100	-0.02800
C	3.45900	1.42600	-0.52900
C	4.82100	1.74200	-0.51000
C	5.34700	-0.40700	0.50800
C	5.75900	0.84300	0.00200
C	1.57700	-0.20800	-0.02600
C	3.97700	-0.72400	0.48200
O	1.22600	-1.33900	0.39100
O	0.75200	0.69600	-0.47100
O	-3.33300	-0.45200	-0.25900
Ag	-1.24400	-0.01700	-0.34700
S	-3.77200	-1.96300	-0.37100
H	-5.43900	-2.97400	-1.73900
H	-5.77200	-1.21000	-1.48100
H	-4.47400	-1.74400	-2.62800
H	-5.64300	-1.40800	1.03700
H	-5.34000	-3.19300	0.93300
H	-4.26700	-2.16200	1.94400
H	2.72700	2.12500	-0.92700
H	5.16200	2.70200	-0.89900
H	3.63200	-1.68600	0.86300
H	5.98900	-2.26300	1.06100
H	7.22200	-1.18100	0.72700
H	6.82000	1.10300	0.01300

_o_-NH_2 CP3 BP

O	1.11500	-1.40500	0.11600
O	0.72500	0.74900	-0.41800
Ag	-1.27600	0.01200	-0.37200
O	-3.32100	-0.61700	-0.32700
S	-4.33500	0.34200	0.40900
C	-5.01900	-0.66600	1.75200
H	-5.82400	-0.08500	2.21900
H	-5.39100	-1.61300	1.34300
H	-4.20800	-0.83000	2.47100
C	-5.78200	0.36200	-0.68200
H	-6.08400	-0.67000	-0.89900
H	-6.57600	0.91300	-0.16100
H	-5.48600	0.89500	-1.59200
C	2.97900	0.11800	0.03100
C	3.38800	1.46000	-0.11100
C	4.71500	1.84900	0.04700
H	2.62400	2.20000	-0.34400
C	5.30600	-0.45900	0.51000
C	5.67500	0.87200	0.36700
H	5.00400	2.89300	-0.06800
C	1.52700	-0.22400	-0.09600
C	3.96200	-0.87400	0.33800
H	6.72000	1.15400	0.50500
H	6.05600	-1.21500	0.75300
N	3.64700	-2.21500	0.42200
H	4.27400	-2.79000	0.97700
H	2.64200	-2.38600	0.52500

_p_-NH_2 CP3 BP

N	7.02600	0.73500	0.70200
C	-5.33700	-2.44100	-0.84100
C	-4.66000	-1.39600	1.61100
C	2.94900	-0.14500	0.02000
C	3.40200	1.18800	0.08200
C	4.74600	1.48300	0.28400
C	5.24500	-0.89200	0.36400
C	5.69500	0.44600	0.43300
C	1.50500	-0.48100	-0.17800
C	3.89900	-1.17500	0.16300
O	1.12900	-1.68300	-0.20200
O	0.69300	0.53400	-0.31000
O	-3.37700	-0.65300	-0.64000
Ag	-1.29900	-0.18300	-0.47200
S	-3.85600	-1.96800	0.08800
H	-5.79700	-3.28600	-0.31300
H	-6.01700	-1.58200	-0.89400
H	-5.00100	-2.75200	-1.83600
H	-5.40600	-0.63200	1.36300
H	-5.12200	-2.27200	2.08500
H	-3.87000	-0.99300	2.25500

H	2.68200	1.99800	-0.02800
H	5.07800	2.52200	0.33200
H	3.56300	-2.21000	0.11100
H	5.96700	-1.70400	0.47300
H	7.69100	0.00300	0.46400
H	7.34400	1.65500	0.40800

***m*-NO_2 CP3 BP**

O	0.86200	-1.32400	-0.42800
O	0.16300	0.83200	-0.44800
Ag	-1.75500	0.01500	-0.82900
O	-3.77700	-0.50900	-1.24600
S	-4.21000	-2.01600	-1.06900
C	-5.05200	-2.41100	-2.62500
H	-5.49000	-3.41100	-2.51500
H	-5.82000	-1.65400	-2.82100
H	-4.28500	-2.41700	-3.40700
C	-5.66200	-1.92800	0.01300
H	-6.37400	-1.20500	-0.40100
H	-6.09400	-2.93600	0.06500
H	-5.30300	-1.61900	1.00100
C	2.47200	0.41600	-0.08700
C	2.74600	1.79000	0.02400
C	3.51800	-0.50400	0.03400
C	4.04800	2.24400	0.25300
H	1.92600	2.49900	-0.07200
C	4.81000	-0.03000	0.26200
C	5.09700	1.33400	0.37400
H	4.24800	3.31100	0.33800
H	6.11800	1.66400	0.55100
C	1.06900	-0.09200	-0.33900
H	3.32100	-1.57000	-0.04900
N	5.90800	-0.99700	0.38600
O	5.64300	-2.21000	0.28600
O	7.05800	-0.56100	0.58600

***o*-NO_2 CP3 BP**

O	0.95300	-0.92600	-0.92300
O	1.12900	0.02900	1.12400
Ag	-0.95700	-0.37800	1.23500
O	-3.04900	-0.72500	1.49600
S	-3.57200	-2.16200	1.10300
C	-5.02200	-1.83500	0.06700
H	-5.50400	-2.80100	-0.13200
H	-5.69500	-1.15000	0.59600
H	-4.65300	-1.39700	-0.86700
C	-4.42100	-2.75800	2.59000
H	-5.15600	-2.01200	2.91300
H	-4.90000	-3.71100	2.32900
H	-3.65000	-2.92000	3.35200
C	3.07200	-0.08100	-0.22900
C	3.37700	1.17000	-0.78800
C	4.15000	-0.95000	0.02900
C	4.69300	1.53300	-1.07500
H	2.56300	1.86400	-1.00000
C	5.47500	-0.59800	-0.25900
C	5.74700	0.64800	-0.81400
H	4.89800	2.51300	-1.50700
H	6.27100	-1.30600	-0.04200
H	6.77500	0.92900	-1.03900
C	1.60500	-0.39500	0.00000
N	3.91300	-2.26800	0.62000
O	4.88900	-3.02200	0.80900
O	2.74200	-2.58100	0.91200

***p*-NO_2 CP3 BP**

O	0.58800	-1.92400	0.07100
O	0.13800	0.29600	-0.01500
Ag	-1.89100	-0.32400	0.00900
O	-3.99800	-0.66000	0.03000
S	-4.50200	-2.15500	-0.01600
C	-5.68900	-2.17600	-1.38700
H	-6.17300	-3.16100	-1.38600
H	-6.41800	-1.36900	-1.24400
H	-5.11300	-2.03800	-2.30800
C	-5.67300	-2.26400	1.36300

H	-6.40200	-1.44800	1.28200
H	-6.15900	-3.24700	1.30300
H	-5.08500	-2.18700	2.28400
C	2.41800	-0.37900	0.01200
C	2.85000	0.95700	-0.03400
C	3.36500	-1.41500	0.04800
C	4.20800	1.26100	-0.04200
H	2.11300	1.75700	-0.06200
C	4.72700	-1.13000	0.04100
C	5.12800	0.20900	-0.00400
H	4.55800	2.29000	-0.07600
C	0.94200	-0.72300	0.02500
H	3.01900	-2.44700	0.08100
H	5.47200	-1.92200	0.06900
N	6.56300	0.52000	-0.00900
O	7.37300	-0.42500	0.04000
O	6.90700	1.71600	-0.06400

_m_-OMe CP3 BP

O	0.84400	-1.26800	-0.01100
O	0.32200	0.93000	0.03600
Ag	-1.63800	0.08600	0.01100
O	-3.60300	-0.74500	-0.00700
S	-4.82700	0.24600	-0.07900
C	-5.81400	-0.16500	1.38600
H	-6.74800	0.40800	1.32400
H	-6.00400	-1.24400	1.40200
H	-5.23300	0.15400	2.25900
C	-5.90000	-0.48300	-1.34400
H	-6.07800	-1.53800	-1.10200
H	-6.83400	0.09200	-1.35200
H	-5.37900	-0.37300	-2.30100
C	2.63100	0.33100	0.01900
C	3.03700	1.67800	0.06300
C	3.59100	-0.68400	-0.02000
C	4.39800	1.98300	0.06800
H	2.28800	2.46600	0.09400
C	4.95800	-0.37000	-0.01600
C	5.36800	0.97200	0.02800
H	4.72200	3.02300	0.10300
H	6.42400	1.23400	0.03300
C	1.17100	-0.05400	0.01400
H	3.27500	-1.72600	-0.05400
O	5.81700	-1.44400	-0.05600
C	7.23200	-1.15300	-0.05900
H	7.52400	-0.62100	0.85600
H	7.73100	-2.12600	-0.09600
H	7.50800	-0.56000	-0.94100

_o_-OMe CP3 BP

O	1.19400	0.01700	1.04400
O	0.57600	-0.12600	-1.12100
Ag	-1.33200	-0.02900	-0.16200
O	-3.27800	0.12900	0.70700
S	-4.49500	-0.26000	-0.22000
C	-5.17500	1.32300	-0.78700
H	-6.10100	1.10500	-1.33400
H	-5.36100	1.97000	0.07900
H	-4.43400	1.76300	-1.46400
C	-5.79000	-0.70900	0.96400
H	-5.91200	0.10300	1.69000
H	-6.71000	-0.87900	0.39100
H	-5.46700	-1.63800	1.44700
C	2.90300	-0.11200	-0.64800
C	3.22400	-0.90700	-1.76000
C	3.95100	0.59000	0.00700
C	4.53800	-1.04500	-2.21300
H	2.41300	-1.43200	-2.26400
C	5.27100	0.46300	-0.45900
C	5.55900	-0.35400	-1.55500
H	4.76000	-1.68100	-3.07000
H	6.07700	1.00400	0.03300
H	6.59200	-0.44200	-1.89400
C	1.47200	-0.05800	-0.17800
O	3.61000	1.39600	1.06000
C	4.66500	2.16200	1.68100

H	5.42500	1.50200	2.12300
H	5.13600	2.84300	0.96000
H	4.17500	2.73900	2.47000

***p*-OMe CP3 BP**

O	0.61300	-1.73600	0.14000
O	0.36300	0.49200	-0.16700
Ag	-1.68900	-0.04900	-0.17800
O	-3.76900	-0.52700	-0.21300
S	-4.77400	0.62000	0.19000
C	-5.68500	-0.05700	1.60400
H	-6.47900	0.65800	1.85300
H	-6.09500	-1.03800	1.33600
H	-4.97100	-0.13200	2.43200
C	-6.08200	0.50800	-1.05900
H	-6.44100	-0.52700	-1.11200
H	-6.88100	1.19700	-0.75800
H	-5.64100	0.83000	-2.00800
C	2.57200	-0.36300	0.05100
C	3.13700	0.91300	-0.09400
C	3.43300	-1.46300	0.23300
C	4.52000	1.10200	-0.06500
H	2.48200	1.77200	-0.23400
C	4.81100	-1.29300	0.26500
C	5.36400	-0.00700	0.11300
H	4.93000	2.10300	-0.18200
C	1.08800	-0.57700	0.01000
H	3.00200	-2.45600	0.34800
H	5.48000	-2.14300	0.40500
O	6.73300	0.06200	0.15100
C	7.33300	1.36600	-0.01800
H	7.02300	2.04600	0.78700
H	8.41200	1.19900	0.03200
H	7.06700	1.79400	-0.99400

***m*-OEt CP3 BP**

O	0.69800	-1.27300	0.00000
O	-0.04300	0.86400	0.00000
Ag	-1.95800	-0.05400	0.00000
O	-3.99300	-0.70700	0.00000
S	-4.27600	-2.25800	0.00000
C	-5.43400	-2.49300	-1.37500
H	-5.78000	-3.53400	-1.33700
H	-6.26700	-1.78800	-1.26700
H	-4.87300	-2.31400	-2.29800
C	-5.43400	-2.49300	1.37500
H	-6.26700	-1.78800	1.26700
H	-5.78000	-3.53400	1.33700
H	-4.87300	-2.31400	2.29800
C	2.31100	0.50400	0.00000
C	2.56300	1.88900	0.00000
C	3.38100	-0.39600	0.00000
C	3.88000	2.34700	0.00000
H	1.72800	2.58700	0.00000
C	4.70500	0.07200	0.00000
C	4.95800	1.45300	0.00000
H	4.08300	3.41800	0.00000
H	5.97600	1.83500	0.00000
C	0.89900	-0.03500	0.00000
H	3.18800	-1.46800	0.00000
O	5.68400	-0.89500	0.00000
C	7.06700	-0.44500	0.00000
H	7.24200	0.17300	0.89300
H	7.24200	0.17300	-0.89300
C	7.95600	-1.67200	0.00000
H	9.00700	-1.35600	0.00000
H	7.78100	-2.28700	0.89400
H	7.78100	-2.28700	-0.89400

***o*-OEt CP3 BP**

O	1.26000	-0.81400	1.18300
O	0.39800	0.46800	-0.47000
Ag	-1.43500	-0.39200	0.15400
O	-3.38200	-1.08300	0.69300
S	-3.97000	-2.25900	-0.17900
C	-5.00700	-1.44900	-1.42900

H	-5.53500	-2.24000	-1.97800
H	-5.70600	-0.76500	-0.93300
H	-4.33100	-0.91300	-2.10500
C	-5.28200	-2.93400	0.87100
H	-5.94400	-2.12000	1.19200
H	-5.82300	-3.68100	0.27400
H	-4.79000	-3.41500	1.72300
C	2.71800	0.66400	-0.03600
C	2.75900	2.04300	-0.29600
C	3.93900	-0.06200	-0.02000
C	3.96400	2.71800	-0.50500
H	1.81500	2.58700	-0.31900
C	5.15100	0.61600	-0.24500
C	5.16000	1.99500	-0.47600
H	3.96800	3.79200	-0.68900
H	6.09100	0.07100	-0.24000
H	6.11300	2.49900	-0.63800
C	1.38200	0.02800	0.26500
O	3.86700	-1.41400	0.18400
C	5.11000	-2.16800	0.13100
H	5.58900	-2.00500	-0.84600
H	5.78800	-1.80200	0.91700
C	4.77300	-3.63000	0.33700
H	4.10100	-3.99600	-0.45200
H	5.69800	-4.22200	0.30400
H	4.29500	-3.79200	1.31300

***p*-OEt CP3 BP**

O	0.27700	-1.92700	0.00000
O	0.00500	0.32000	0.00000
Ag	-2.05500	-0.18000	0.00000
O	-4.18000	-0.39600	0.00000
S	-4.76600	-1.86000	0.00000
C	-5.94600	-1.85900	-1.37600
H	-6.48900	-2.81300	-1.34400
H	-6.62500	-1.00500	-1.26700
H	-5.35600	-1.79000	-2.29700
C	-5.94600	-1.85900	1.37600
H	-6.62500	-1.00500	1.26700
H	-6.48900	-2.81300	1.34400
H	-5.35600	-1.79000	2.29700
C	2.22300	-0.53400	0.00000
C	2.76800	0.76000	0.00000
C	3.10400	-1.63200	0.00000
C	4.14900	0.96600	0.00000
H	2.09800	1.61700	0.00000
C	4.48100	-1.44500	0.00000
C	5.01400	-0.14100	0.00000
H	4.54000	1.98100	0.00000
C	0.74000	-0.75800	0.00000
H	2.69300	-2.64100	0.00000
H	5.16400	-2.29500	0.00000
O	6.38000	-0.05300	0.00000
C	6.96900	1.27900	0.00000
H	6.62400	1.82000	0.89300
H	6.62400	1.82000	-0.89300
C	8.47500	1.11900	0.00000
H	8.81500	0.57800	-0.89400
H	8.94200	2.11300	0.00000
H	8.81500	0.57800	0.89400

***m*-OH CP3 BP**

O	1.38200	-1.51000	-0.00500
O	0.75300	0.66400	0.00000
Ag	-1.21100	-0.13700	0.00300
O	-3.29100	-0.62000	0.00800
S	-3.70600	-2.14100	-0.00500
C	-4.88400	-2.26300	-1.37600
H	-5.31300	-3.27300	-1.35000
H	-5.65700	-1.49400	-1.25600
H	-4.31300	-2.11700	-2.29900
C	-4.87200	-2.28900	1.37500
H	-5.64700	-1.52000	1.27600
H	-5.30000	-3.29900	1.33500
H	-4.29200	-2.16100	2.29600
C	3.08400	0.18200	-0.00600

C	3.41000	1.54800	-0.01300
C	4.75200	1.94100	-0.01100
H	2.61400	2.29000	-0.01900
C	5.44600	-0.37300	0.00700
C	5.77500	0.98900	-0.00100
H	5.01000	3.00000	-0.01700
C	1.64600	-0.28300	-0.00300
H	6.82400	1.28600	0.00200
C	4.10700	-0.77900	0.00300
O	6.48800	-1.27900	0.02000
H	6.11100	-2.18100	0.02700
H	3.84800	-1.83900	0.00800

***o*-OH CP3 BP**

O	1.51200	-1.45200	-0.02400
O	0.88000	0.71700	-0.05500
Ag	-1.09500	-0.06300	-0.08700
O	-3.17500	-0.54200	-0.08800
S	-3.59000	-2.01900	-0.46000
C	-4.76900	-1.81300	-1.82100
H	-5.20200	-2.79900	-2.03400
H	-5.54000	-1.09200	-1.52300
H	-4.19800	-1.45600	-2.68600
C	-4.75900	-2.48100	0.84400
H	-5.53700	-1.71200	0.92100
H	-5.18400	-3.45700	0.57300
H	-4.18200	-2.56500	1.77200
C	3.21200	0.22300	-0.01700
C	3.57300	1.58500	-0.03000
C	4.91000	1.97400	-0.00900
H	2.77800	2.32900	-0.05600
C	5.58800	-0.36200	0.03700
C	5.91500	0.99200	0.02500
H	5.17500	3.03100	-0.02000
C	1.78400	-0.20300	-0.03300
H	6.96400	1.28800	0.04200
C	4.24000	-0.76000	0.01600
H	6.36100	-1.13100	0.06200
O	3.94100	-2.08500	0.02600
H	2.90900	-2.08800	0.00400

***p*-OH CP3 BP**

O	1.28600	-1.62300	-0.79700
O	0.73000	0.32000	0.22200
Ag	-1.24300	-0.35400	-0.15400
O	-3.29900	-0.80000	-0.51500
S	-3.90500	-2.01400	0.29000
C	-5.21500	-2.62200	-0.80100
H	-5.76900	-3.39300	-0.25000
H	-5.86400	-1.78500	-1.08500
H	-4.72100	-3.06300	-1.67400
C	-4.94000	-1.25400	1.57000
H	-5.62700	-0.53700	1.10300
H	-5.48300	-2.06300	2.07600
H	-4.26200	-0.75900	2.27400
C	3.04100	-0.16900	-0.06200
C	3.42100	1.03100	0.56800
C	4.76300	1.37000	0.71800
H	2.65000	1.70300	0.94200
C	5.39500	-0.70000	-0.39700
C	5.75300	0.50200	0.23200
H	5.06000	2.29900	1.20500
C	1.59700	-0.54200	-0.23600
C	4.04800	-1.02600	-0.53900
H	3.76100	-1.95700	-1.02700
H	6.17200	-1.36900	-0.77000
O	7.06500	0.87900	0.39800
H	7.63700	0.18600	0.01300

***m*-O^{i}Pr CP3 BP**

O	-0.47300	1.64200	0.00000
O	-0.07400	-0.58300	0.00000
Ag	-2.20300	-0.63600	0.00000
O	-4.33300	-0.87000	0.00000
S	-5.15300	0.47800	0.00000
C	-6.31500	0.29600	1.37700

H	-6.98900	1.16300	1.34900
H	-6.86500	-0.64600	1.26800
H	-5.72100	0.31100	2.29700
C	-6.31500	0.29600	-1.37700
H	-6.86500	-0.64600	-1.26800
H	-6.98900	1.16300	-1.34900
H	-5.72100	0.31100	-2.29700
C	1.80200	0.89300	0.00000
C	2.30300	2.20800	0.00000
C	2.69100	-0.18600	0.00000
C	3.68100	2.41400	0.00000
H	1.60700	3.04500	0.00000
C	4.08300	0.02200	0.00000
C	4.57800	1.33700	0.00000
H	4.08000	3.42900	0.00000
H	5.64500	1.53800	0.00000
C	0.31100	0.66100	0.00000
H	2.31000	-1.20700	0.00000
O	4.82200	-1.13600	0.00000
C	6.29500	-1.16600	0.00000
H	6.46200	-2.25100	0.00000
C	6.89500	-0.61000	1.28800
H	7.95400	-0.90000	1.33500
H	6.84700	0.48400	1.35000
H	6.38900	-1.03700	2.16300
C	6.89500	-0.61000	-1.28800
H	6.38900	-1.03700	-2.16300
H	6.84700	0.48400	-1.35000
H	7.95400	-0.90000	-1.33500

***o*-O^{i}Pr CP3 BP**

O	0.24200	1.94200	0.00000
O	0.41400	-0.30900	0.00000
Ag	-1.69200	-0.29400	0.00000
O	-3.78800	-0.67400	0.00000
S	-4.77600	0.55500	0.00000
C	-5.90300	0.21100	1.37600
H	-6.69500	0.97100	1.35000
H	-6.31200	-0.80000	1.26300
H	-5.31700	0.30600	2.29700
C	-5.90300	0.21100	-1.37600
H	-6.31200	-0.80000	-1.26300
H	-6.69500	0.97100	-1.35000
H	-5.31700	0.30600	-2.29700
C	2.43900	0.98700	0.00000
C	2.97900	2.28600	0.00000
C	3.34300	-0.12200	0.00000
C	4.35100	2.53000	0.00000
H	2.27100	3.11400	0.00000
C	4.73000	0.13500	0.00000
C	5.22600	1.43900	0.00000
H	4.73200	3.55100	0.00000
H	5.43400	-0.69100	0.00000
H	6.30500	1.59400	0.00000
C	0.92600	0.88300	0.00000
O	2.80100	-1.36800	0.00000
C	3.58100	-2.61800	0.00000
H	2.75700	-3.34300	0.00000
C	4.37000	-2.83200	1.29000
H	3.73800	-2.62100	2.16300
H	4.67300	-3.88800	1.34000
H	5.27700	-2.22000	1.35400
C	4.37000	-2.83200	-1.29000
H	5.27700	-2.22000	-1.35400
H	4.67300	-3.88800	-1.34000
H	3.73800	-2.62100	-2.16300

***p*-O^{i}Pr CP3 BP**

O	-0.24400	0.99800	0.00000
O	-0.37600	-1.25900	0.00000
Ag	-2.45300	-0.78400	0.00000
O	-4.57400	-0.48600	0.00000
S	-5.06700	1.01200	0.00000
C	-6.24300	1.09700	1.37600
H	-6.71200	2.08900	1.34300
H	-6.98500	0.29700	1.26800

H	-5.66200	0.98500	2.29700
C	-6.24300	1.09700	-1.37600
H	-6.98500	0.29700	-1.26800
H	-6.71200	2.08900	-1.34300
H	-5.66200	0.98500	-2.29700
C	1.78800	-0.26400	0.00000
C	2.58900	0.88900	0.00000
C	2.42900	-1.51800	0.00000
C	3.98200	0.81400	0.00000
H	2.10500	1.86500	0.00000
C	3.81500	-1.60900	0.00000
C	4.61300	-0.44500	0.00000
H	4.56000	1.73300	0.00000
C	0.29500	-0.13900	0.00000
H	1.82800	-2.42500	0.00000
H	4.31100	-2.58100	0.00000
O	5.96000	-0.68600	0.00000
C	6.98800	0.37500	0.00000
H	7.89500	-0.24300	0.00000
C	6.98600	1.19300	1.28700
H	6.96800	0.53100	2.16300
H	7.91500	1.78100	1.32800
H	6.14500	1.89300	1.35500
C	6.98600	1.19300	-1.28700
H	6.96800	0.53100	-2.16300
H	6.14500	1.89300	-1.35500
H	7.91500	1.78100	-1.32800

H CP3 BP

O	1.19300	-1.37300	0.00000
O	1.13300	0.88800	0.00000
Ag	-0.96900	0.60300	0.00000
O	-3.10300	0.65500	0.00000
S	-3.86600	-0.72600	0.00000
C	-5.03800	-0.58200	-1.37600
H	-5.69000	-1.46500	-1.34300
H	-5.61100	0.34600	-1.26500
H	-4.44700	-0.58200	-2.29800
C	-5.03800	-0.58200	1.37600
H	-5.61100	0.34600	1.26500
H	-5.69000	-1.46500	1.34300
H	-4.44700	-0.58200	2.29800
C	3.26800	-0.17200	0.00000
C	3.93300	1.06700	0.00000
C	4.02400	-1.35600	0.00000
C	5.33000	1.11800	0.00000
H	3.34700	1.98500	0.00000
C	5.42000	-1.30600	0.00000
H	3.50100	-2.31300	0.00000
C	6.07500	-0.06800	0.00000
H	5.83900	2.08300	0.00000
H	5.99800	-2.23000	0.00000
H	7.16600	-0.02800	0.00000
C	1.76000	-0.25300	0.00000

***o*-Br+*m*-NO_2 CP3 BP**

O	1.03700	-0.98100	-0.70900
O	0.30500	0.78900	0.50600
Ag	-1.59900	-0.14400	0.39200
O	-3.61000	-0.85400	0.42300
S	-4.01200	-1.97200	-0.61600
C	-5.41900	-1.25900	-1.50900
H	-5.82800	-2.04500	-2.15700
H	-6.16300	-0.90500	-0.78600
H	-5.02500	-0.43700	-2.11700
C	-4.91000	-3.18600	0.38600
H	-5.68900	-2.67200	0.96200
H	-5.34000	-3.92500	-0.30200
H	-4.17400	-3.66300	1.04200
C	2.56900	0.78300	-0.16300
C	2.60400	2.16000	-0.41500
C	3.79900	0.11900	0.00200
C	3.82500	2.82300	-0.52800
H	1.67200	2.70900	-0.52800
C	5.02200	0.79600	-0.09100
C	5.04400	2.15700	-0.36800

H	5.95500	0.25500	0.05600
H	5.98400	2.69600	-0.45300
C	1.20900	0.10900	-0.12600
Br	3.89200	-1.75100	0.43400
N	3.82800	4.25800	-0.80800
O	4.92800	4.83700	-0.89700
O	2.73300	4.83900	-0.94400

***o*-Cl+*m*-NO_2 CP3 BP**

O	1.33400	-0.31000	-1.29500
O	1.13900	-0.12900	0.95800
Ag	-0.92500	0.15700	0.52200
O	-2.96900	0.66800	0.19900
S	-4.01400	-0.50600	0.06500
C	-4.43600	-0.54700	-1.69900
H	-5.25100	-1.27100	-1.82400
H	-4.73400	0.45700	-2.02500
H	-3.54200	-0.89200	-2.23200
C	-5.54400	0.22800	0.69500
H	-5.72600	1.17900	0.18100
H	-6.35200	-0.49200	0.50900
H	-5.40600	0.37100	1.77200
C	3.31600	-0.26500	0.04700
C	3.87300	0.69600	0.89700
C	4.19600	-1.13400	-0.62900
C	5.25700	0.79700	1.02800
H	3.22200	1.37000	1.44800
C	5.58500	-1.03700	-0.47500
C	6.12700	-0.05900	0.34900
H	6.23300	-1.73100	-1.00500
H	7.20300	0.03800	0.46900
C	1.81200	-0.25500	-0.14300
Cl	3.59300	-2.41700	-1.65800
N	5.81000	1.82400	1.91100
O	7.04900	1.88800	2.03500
O	5.02000	2.58700	2.50100

***o*-F+*m*-NO_2 CP3 BP**

O	1.48900	-1.58500	0.04300
O	0.92800	0.60800	0.05400
Ag	-1.05700	-0.15500	0.06100
O	-3.13400	-0.64500	0.07100
S	-3.53200	-2.16900	-0.01800
C	-4.71300	-2.23200	-1.39100
H	-5.13300	-3.24600	-1.41700
H	-5.49300	-1.47900	-1.22900
H	-4.14600	-2.03400	-2.30700
C	-4.69500	-2.39500	1.35400
H	-5.46800	-1.62000	1.29900
H	-5.12500	-3.40000	1.25700
H	-4.11400	-2.31900	2.27900
C	3.23300	0.07300	0.03100
C	3.54100	1.43800	-0.01800
C	4.32300	-0.81600	0.06300
C	4.86700	1.86400	-0.03500
H	2.73000	2.16000	-0.04300
C	5.65300	-0.39500	0.04800
C	5.93700	0.96200	-0.00200
H	6.44700	-1.14000	0.07600
H	6.96300	1.32200	-0.01500
C	1.78300	-0.37000	0.04400
F	4.11900	-2.15400	0.11200
N	5.14900	3.29800	-0.09100
O	4.18800	4.09100	-0.12200
O	6.34100	3.66400	-0.10500

A.1.3. Cartesian geometries of TS compounds at BP/TZP level of computation.

***m*-Br TS BP**

O	-2.31000	-0.39400	1.04600
O	-2.27200	-0.48500	-1.26800
Ag	0.54300	0.20500	-0.09300
O	1.47400	2.13600	-0.15900
S	0.69800	3.48000	0.06900
C	-0.22700	3.26300	1.61300
H	-0.84900	4.15600	1.75700
H	-0.84400	2.35700	1.54000
H	0.51200	3.18200	2.41700
C	-0.70000	3.45800	-1.08300
H	-1.27400	2.53300	-0.93900
H	-1.31500	4.34300	-0.87500
H	-0.28200	3.51500	-2.09400
C	-0.18800	-1.78500	-0.02800
C	-0.04600	-2.44100	1.21600
C	0.00500	-2.53200	-1.21000
C	0.31400	-3.78700	1.24500
C	0.37000	-3.88100	-1.15800
H	-0.15100	-2.05700	-2.18000
C	0.53000	-4.52300	0.07700
H	0.52300	-4.44700	-2.07800
H	0.80000	-5.57700	0.12400
C	-1.95600	-0.57900	-0.10000
H	-0.23900	-1.90600	2.14700
Br	0.51000	-4.68200	2.96600

***o*-Br TS BP**

O	-1.63900	-0.88100	-1.30900
O	0.52400	-1.03500	-2.10200
Ag	0.63000	0.33500	0.67800
O	1.12500	2.40500	0.96500
S	0.79100	3.49500	-0.11400
C	-0.95900	3.26200	-0.52400
H	-1.20500	3.94500	-1.34700
H	-1.12300	2.21500	-0.81500
H	-1.53300	3.52300	0.37100
C	1.50900	2.89400	-1.66500
H	1.15100	1.87200	-1.85500
H	1.19900	3.57800	-2.46500
H	2.59700	2.92000	-1.54300
C	0.20700	-1.74600	0.48200
C	-0.72600	-2.25100	1.40900
C	1.33100	-2.57100	0.23000
C	-0.58300	-3.48100	2.05000
C	1.51500	-3.79900	0.86900
H	2.05500	-2.23800	-0.51500
C	0.55000	-4.25800	1.77200
H	-1.33300	-3.83100	2.75900
H	2.39600	-4.40300	0.65300
H	0.66700	-5.22400	2.26400
C	-0.43400	-1.03300	-1.34900
Br	-2.29400	-1.19000	1.90400

***p*-Br TS BP**

O	-2.34900	0.92700	1.19800
O	-2.36200	0.94400	-1.11900
Ag	0.52200	1.34500	0.02700
O	1.57600	3.21700	0.03400
S	0.85800	4.61100	-0.03100
C	-0.38700	4.59400	1.28500
H	-0.98400	5.51100	1.19200
H	-1.01500	3.69900	1.17600
H	0.15600	4.58900	2.23700
C	-0.26100	4.53100	-1.45500
H	-0.90200	3.64400	-1.36000
H	-0.85800	5.45200	-1.46200
H	0.36700	4.47800	-2.35000
C	-0.35800	-0.58000	0.01600
C	-0.25400	-1.31400	1.21800
C	-0.27400	-1.29700	-1.19700
C	-0.03600	-2.69700	1.22000
C	-0.05600	-2.68000	-1.22200
H	-0.40000	-0.77500	-2.14700
C	0.06400	-3.35800	-0.00700
H	0.00900	-3.21500	-2.16900

C	-2.03200	0.77000	0.03600
H	-0.36200	-0.80600	2.17800
H	0.04600	-3.24600	2.15700
Br	0.35300	-5.27700	-0.02300

***m*-CF_3 TS BP**

O	-2.66700	-0.61100	0.15100
O	-2.06000	-1.06300	-2.04000
Ag	0.28800	0.26100	-0.45000
O	0.98500	2.28100	-0.64100
S	0.91400	3.31200	0.54000
C	1.73100	2.50600	1.94200
H	1.62600	3.16300	2.81500
H	1.25800	1.53000	2.12100
H	2.78700	2.39500	1.67500
C	-0.78900	3.24300	1.15800
H	-1.04300	2.20000	1.39100
H	-0.84500	3.87400	2.05500
H	-1.43200	3.64500	0.36900
C	-0.20100	-1.78000	-0.14800
C	-0.28600	-2.17900	1.20200
C	0.36300	-2.68600	-1.07100
C	0.21700	-3.41800	1.61400
C	0.86600	-3.92500	-0.65900
H	0.39500	-2.42500	-2.13100
C	0.80200	-4.29400	0.68700
H	1.30300	-4.61000	-1.38600
H	1.18400	-5.26300	1.01000
C	-2.02700	-0.91500	-0.83500
H	-0.77200	-1.52800	1.93000
C	0.17000	-3.81000	3.06400
F	-0.77400	-3.12500	3.77100
F	1.37100	-3.57300	3.70100
F	-0.08800	-5.14300	3.24100

***o*-CF_3 TS BP**

O	-2.43700	-0.92700	-0.74000
O	-0.91300	-1.47000	-2.39100
Ag	0.60100	0.22000	-0.31400
O	1.36800	2.17400	-0.76400
S	0.89700	2.99500	-2.01600
C	-0.91000	3.07700	-1.90800
H	-1.27700	3.56200	-2.82200
H	-1.31300	2.06000	-1.81000
H	-1.14900	3.68900	-1.03200
C	1.02600	1.86500	-3.42700
H	0.46200	0.94700	-3.20800
H	0.61800	2.38100	-4.30600
H	2.09200	1.65600	-3.57000
C	-0.00100	-1.78100	0.14400
C	-0.41000	-2.05900	1.47600
C	0.86900	-2.71900	-0.45700
C	0.02700	-3.20700	2.14900
C	1.33200	-3.85200	0.21800
H	1.15900	-2.56300	-1.49700
C	0.90200	-4.10100	1.52400
H	-0.30600	-3.40300	3.16800
H	2.01300	-4.54400	-0.27800
H	1.23800	-4.98900	2.05800
C	-1.40600	-1.23600	-1.30200
C	-1.36600	-1.17100	2.24000
F	-1.04400	-1.10900	3.57400
F	-1.41300	0.11900	1.80300
F	-2.65600	-1.64400	2.19500

***p*-CF_3 TS BP**

O	-2.32200	0.90900	1.15800
O	-2.32200	0.90900	-1.15800
Ag	0.54900	1.28000	0.00000
O	1.61700	3.14100	0.00000
S	0.87200	4.52300	0.00000
C	-0.31000	4.44800	1.37200
H	-0.92800	5.35400	1.33200
H	-0.92600	3.54400	1.26700
H	0.27600	4.42700	2.29700
C	-0.31000	4.44800	-1.37200

H	-0.92600	3.54400	-1.26700
H	-0.92800	5.35400	-1.33200
H	0.27600	4.42700	-2.29700
C	-0.36300	-0.63000	0.00000
C	-0.26800	-1.35000	1.21000
C	-0.26800	-1.35000	-1.21000
C	-0.04400	-2.72900	1.21800
C	-0.04400	-2.72900	-1.21800
H	-0.39000	-0.83100	-2.16200
C	0.06600	-3.41400	0.00000
H	0.03100	-3.26800	-2.16200
C	-1.99600	0.73800	0.00000
H	-0.39000	-0.83100	2.16200
H	0.03100	-3.26800	2.16200
C	0.34000	-4.89100	0.00000
F	-0.17000	-5.52300	1.09800
F	-0.17000	-5.52300	-1.09800
F	1.69200	-5.16100	0.00000

***m*-CH_3 TS BP**

O	-2.52200	-0.42200	0.40100
O	-2.10100	-0.83500	-1.84000
Ag	0.41800	0.23600	-0.37500
O	1.18600	2.23400	-0.57500
S	0.76200	3.39800	0.38800
C	1.00400	2.76000	2.06700
H	0.63300	3.51700	2.77000
H	0.45200	1.81600	2.17300
H	2.08100	2.61200	2.19900
C	-1.05000	3.42300	0.37600
H	-1.42800	2.42200	0.62500
H	-1.37800	4.16600	1.11500
H	-1.35700	3.72800	-0.63000
C	-0.13800	-1.77900	-0.09100
C	-0.16300	-2.22300	1.24900
C	0.25600	-2.69500	-1.08800
C	0.23300	-3.51900	1.61600
C	0.64800	-3.99400	-0.74400
H	0.24000	-2.39900	-2.13900
C	0.64000	-4.40000	0.59500
H	0.95200	-4.69700	-1.52100
H	0.93700	-5.41900	0.85200
C	-1.97300	-0.72500	-0.63800
H	-0.52000	-1.54700	2.03200
C	0.23100	-3.95900	3.06200
H	-0.23400	-4.94800	3.17900
H	-0.31100	-3.24500	3.69600
H	1.25800	-4.03900	3.45000

***o*-CH_3 TS BP**

O	-2.76400	-1.04600	-0.39700
O	-1.49400	-1.35000	-2.30400
Ag	0.09500	0.32400	-0.33300
O	0.51800	2.41100	-0.63300
S	1.03300	3.35300	0.50900
C	2.44200	2.49400	1.25600
H	2.77500	3.08100	2.12100
H	2.12700	1.48500	1.55700
H	3.22900	2.45400	0.49500
C	-0.14200	3.16800	1.87600
H	-0.24100	2.10200	2.12300
H	0.24600	3.73900	2.73000
H	-1.09400	3.59100	1.53900
C	-0.11000	-1.75400	0.05100
C	-0.33100	-2.11800	1.40800
C	0.68400	-2.59800	-0.75700
C	0.25100	-3.29900	1.89900
C	1.27700	-3.75700	-0.24800
H	0.81400	-2.35000	-1.81200
C	1.05400	-4.10900	1.08800
H	0.07700	-3.58500	2.93900
H	1.89200	-4.38900	-0.89100
H	1.49400	-5.02000	1.49800
C	-1.81200	-1.21200	-1.13700
C	-1.13800	-1.24900	2.34600
H	-1.57800	-1.84000	3.16000

H	-0.49700	-0.48500	2.81200
H	-1.93800	-0.73000	1.80600

p-CH_3 TS BP

O	-2.25800	-0.10400	1.28600
O	-2.31500	-0.01200	-1.03000
Ag	0.56200	0.51300	0.07700
O	1.48700	2.45400	0.11400
S	0.68000	3.78400	-0.08600
C	-0.66500	3.74000	1.12900
H	-1.31400	4.60500	0.93900
H	-1.21800	2.79700	1.02300
H	-0.20200	3.82200	2.11800
C	-0.31000	3.54500	-1.58600
H	-0.89200	2.61800	-1.48900
H	-0.96800	4.41800	-1.69400
H	0.39200	3.49200	-2.42400
C	-0.16500	-1.46200	0.02100
C	-0.01600	-2.23300	1.19400
C	-0.07600	-2.13900	-1.21500
C	0.24800	-3.60500	1.13400
C	0.18800	-3.51000	-1.27600
H	-0.23000	-1.59000	-2.14700
C	0.35600	-4.26900	-0.10200
H	0.25900	-4.00500	-2.24800
C	-1.95800	-0.19200	0.11500
H	-0.12100	-1.75900	2.17200
H	0.36700	-4.17500	2.05900
C	0.60200	-5.75600	-0.16900
H	1.06600	-6.12700	0.75400
H	-0.34500	-6.30200	-0.30500
H	1.24800	-6.01600	-1.01900

***o*-Cl+*o*-Me TS BP**

O	-2.11900	-0.28600	-1.60800
O	-0.28100	-1.18700	-2.64900
Ag	0.31900	0.28500	0.27600
O	1.07600	2.24900	0.71200
S	0.57400	3.52200	-0.05600
C	-1.23600	3.44400	-0.01000
H	-1.62400	4.27200	-0.61800
H	-1.56300	2.47300	-0.40800
H	-1.53300	3.57100	1.03700
C	0.80700	3.16500	-1.81700
H	0.31300	2.21400	-2.06000
H	0.36900	3.99400	-2.38700
H	1.88700	3.11100	-1.99000
C	-0.46500	-1.68900	-0.05200
C	-1.57500	-2.04800	0.77700
C	0.55800	-2.66300	-0.18300
C	-1.63500	-3.32800	1.35400
C	0.49800	-3.93300	0.38100
C	-0.62500	-4.26600	1.14600
H	-2.48600	-3.58500	1.98700
H	1.31600	-4.63800	0.24400
H	-0.69300	-5.25600	1.59600
C	-1.05100	-0.86600	-1.75600
C	-2.70800	-1.09200	1.07100
H	-3.03600	-1.21400	2.11300
H	-3.57200	-1.30100	0.42500
H	-2.42300	-0.04900	0.91100
Cl	2.05400	-2.26900	-1.05800

***o*-Cl+*o*-NO_2 TS BP**

O	-0.14700	-0.57000	2.56800
O	-1.04700	1.50400	2.14800
Ag	0.66400	0.26600	-0.41900
O	2.66700	0.53800	-1.16900
S	3.77300	-0.56900	-1.06600
C	3.03500	-2.06100	-1.78500
H	3.73600	-2.89200	-1.63600
H	2.07500	-2.25700	-1.28700
H	2.89700	-1.86500	-2.85300
C	3.78800	-1.09200	0.66800
H	2.76300	-1.35300	0.97000
H	4.46000	-1.95600	0.75600

H	4.17100	-0.24900	1.25300
C	-1.34400	-0.25000	0.19700
C	-1.65700	-1.63500	0.13600
C	-2.32300	0.62600	-0.33800
C	-2.88400	-2.05600	-0.41900
C	-3.54900	0.22400	-0.85400
C	-3.82300	-1.14700	-0.89800
H	-3.10000	-3.12500	-0.46900
H	-4.24900	0.95900	-1.24900
H	-4.76400	-1.49700	-1.32000
C	-0.68200	0.35100	1.97100
C	-0.71800	-2.70300	0.64400
H	-0.56100	-3.45900	-0.13800
H	-1.14900	-3.22300	1.51200
H	0.24900	-2.29200	0.94400
N	-2.04700	2.07300	-0.39900
O	-0.88300	2.45200	-0.64700
O	-2.99600	2.86000	-0.23600

***m*-CN TS BP**

O	-2.44100	-0.39700	0.60100
O	-2.20000	-0.78000	-1.67100
Ag	0.46400	0.20800	-0.33500
O	1.30600	2.17500	-0.46200
S	0.75600	3.38200	0.37700
C	0.68900	2.79900	2.09100
H	0.23100	3.59100	2.69700
H	0.09400	1.87500	2.13400
H	1.72200	2.62500	2.40900
C	-1.02500	3.44900	0.05200
H	-1.47000	2.46700	0.26800
H	-1.45200	4.22600	0.69900
H	-1.14600	3.72200	-1.00200
C	-0.20000	-1.79700	-0.11500
C	-0.13000	-2.28500	1.20100
C	0.13000	-2.67800	-1.16800
C	0.30200	-3.60200	1.45500
C	0.55800	-3.98700	-0.91900
H	0.03300	-2.33900	-2.20100
C	0.65100	-4.45700	0.39000
H	0.81200	-4.64800	-1.74800
H	0.97500	-5.47600	0.59700
C	-1.98000	-0.71000	-0.47900
H	-0.43000	-1.65700	2.04100
C	0.37700	-4.07400	2.80200
N	0.44100	-4.45000	3.90400

***o*-CN TS BP**

O	-2.74500	-0.90600	-0.04900
O	-1.79100	-1.30000	-2.11900
Ag	0.23900	0.29800	-0.38800
O	0.84400	2.33300	-0.66900
S	0.98900	3.34900	0.51700
C	2.06600	2.53900	1.72700
H	2.11000	3.17700	2.61900
H	1.65200	1.54900	1.96600
H	3.05500	2.45700	1.26600
C	-0.56600	3.25900	1.44300
H	-0.76000	2.21300	1.72200
H	-0.46100	3.89300	2.33300
H	-1.35100	3.65100	0.78800
C	-0.18500	-1.75900	-0.01000
C	-0.24900	-2.10500	1.37200
C	0.50500	-2.65500	-0.85000
C	0.36200	-3.26800	1.87600
C	1.12700	-3.80600	-0.35600
H	0.52800	-2.45300	-1.92200
C	1.05300	-4.11400	1.00600
H	0.29600	-3.49800	2.93900
H	1.66000	-4.47100	-1.03600
H	1.52300	-5.01800	1.39400
C	-1.93300	-1.15500	-0.91900
C	-0.92800	-1.25600	2.30600
N	-1.45100	-0.58300	3.10300

***p*-CN TS BP**

O	-2.31700	0.33100	1.15800
O	-2.31700	0.33100	-1.15800
Ag	0.56100	0.76200	0.00000
O	1.61000	2.63400	0.00000
S	0.85400	4.01000	0.00000
C	-0.32700	3.92600	1.37200
H	-0.93700	4.83800	1.34500
H	-0.95000	3.02900	1.25500
H	0.26100	3.88700	2.29500
C	-0.32700	3.92600	-1.37200
H	-0.95000	3.02900	-1.25500
H	-0.93700	4.83800	-1.34500
H	0.26100	3.88700	-2.29500
C	-0.34200	-1.15400	0.00000
C	-0.22400	-1.87000	1.21200
C	-0.22400	-1.87000	-1.21200
C	0.04900	-3.23700	1.22400
C	0.04900	-3.23700	-1.22400
H	-0.36500	-1.35400	-2.16200
C	0.19100	-3.92100	0.00000
H	0.14500	-3.77900	-2.16400
C	-1.98800	0.16300	0.00000
H	-0.36500	-1.35400	2.16200
H	0.14500	-3.77900	2.16400
C	0.45700	-5.32400	0.00000
N	0.67500	-6.47100	0.00000

***m*-CHO TS BP**

O	-2.26400	-0.42300	1.30500
O	-2.31200	-0.36100	-1.01000
Ag	0.55300	0.23300	0.11000
O	1.48200	2.16700	0.10700
S	0.68100	3.48900	-0.16500
C	-0.68700	3.49300	1.02300
H	-1.32900	4.35300	0.79100
H	-1.24200	2.54900	0.93800
H	-0.24500	3.60700	2.01900
C	-0.27800	3.18900	-1.67300
H	-0.87200	2.27300	-1.54600
H	-0.92500	4.06100	-1.83700
H	0.44200	3.09000	-2.49300
C	-0.20000	-1.74700	0.05600
C	-0.02200	-2.50700	1.22400
C	-0.06500	-2.40700	-1.19100
C	0.32000	-3.87100	1.15400
C	0.27900	-3.76000	-1.27200
H	-0.25200	-1.85200	-2.11200
C	0.47400	-4.49300	-0.10000
H	0.38400	-4.24300	-2.24400
H	0.73100	-5.55300	-0.14400
C	-1.95100	-0.53300	0.13700
H	-0.16500	-2.05600	2.20800
C	0.51300	-4.68300	2.36700
H	0.78100	-5.74600	2.17600
O	0.40200	-4.27200	3.52500

***o*-CHO TS BP**

O	-2.72800	-0.98100	-0.05000
O	-1.74000	-1.18500	-2.12700
Ag	0.23500	0.29900	-0.31600
O	0.92700	2.31000	-0.68100
S	1.00400	3.39900	0.44400
C	1.87800	2.61900	1.82600
H	1.88100	3.32700	2.66500
H	1.36000	1.68700	2.09400
H	2.90100	2.42700	1.48700
C	-0.64900	3.46700	1.18400
H	-0.93600	2.45800	1.51100
H	-0.60400	4.16400	2.03100
H	-1.32600	3.85100	0.41300
C	-0.14100	-1.78400	-0.01500
C	-0.16800	-2.14400	1.36500
C	0.44800	-2.70200	-0.90200
C	0.35100	-3.37500	1.80400
C	1.01600	-3.90500	-0.45500
H	0.42600	-2.48900	-1.97200

C	0.96100	-4.24900	0.89900
H	0.29700	-3.62900	2.86400
H	1.47800	-4.58500	-1.17100
H	1.38000	-5.19300	1.24700
C	-1.88600	-1.12900	-0.91600
C	-0.68900	-1.24900	2.41200
H	-0.90100	-1.74300	3.38500
O	-0.87100	-0.03300	2.29300

***p*-CHO TS BP**

O	-2.15000	-0.23000	2.39200
O	-2.95300	0.23000	0.26700
Ag	0.07400	0.96000	0.55500
O	0.93900	2.92400	0.56800
S	1.33200	3.65600	-0.76400
C	-0.12800	3.55700	-1.83200
H	0.14000	3.98500	-2.80600
H	-0.43200	2.50500	-1.93100
H	-0.91200	4.15700	-1.35800
C	2.39700	2.49700	-1.66000
H	1.87400	1.53500	-1.75700
H	2.61400	2.93000	-2.64500
H	3.31800	2.39400	-1.07700
C	-0.53700	-1.05800	0.33900
C	0.08400	-1.97500	1.22100
C	-0.76100	-1.45900	-0.99700
C	0.51900	-3.22000	0.77500
C	-0.32700	-2.70200	-1.45200
H	-1.28800	-0.79300	-1.68200
C	0.32100	-3.58900	-0.57100
H	-0.48800	-3.00100	-2.49000
C	-2.22900	-0.09400	1.18700
H	0.21800	-1.70500	2.27000
H	1.01300	-3.91800	1.45200
C	0.76500	-4.89300	-1.08900
H	0.55700	-5.06000	-2.16900
O	1.32500	-5.76800	-0.42300

***m*-Cl TS BP**

O	-2.30000	-0.39700	1.11600
O	-2.29200	-0.44300	-1.20100
Ag	0.55400	0.20000	-0.04700
O	1.49500	2.12800	-0.06900
S	0.68900	3.47000	0.04400
C	-0.40900	3.27400	1.47100
H	-1.05500	4.16000	1.52100
H	-1.00200	2.35700	1.34700
H	0.23000	3.22000	2.35900
C	-0.56400	3.41100	-1.26400
H	-1.14200	2.48000	-1.16800
H	-1.21000	4.29100	-1.14800
H	-0.03100	3.45400	-2.21900
C	-0.19300	-1.78000	-0.01100
C	-0.03600	-2.45300	1.22100
C	-0.02500	-2.51500	-1.20400
C	0.31600	-3.80200	1.23100
C	0.32900	-3.86800	-1.17300
H	-0.19400	-2.02900	-2.16600
C	0.50500	-4.52400	0.05100
H	0.46000	-4.42500	-2.10100
H	0.77000	-5.58100	0.08700
C	-1.96600	-0.56000	-0.03800
H	-0.20700	-1.93400	2.16500
Cl	0.51700	-4.63400	2.78700

***m*-Cl TS BP**

O	-2.77500	-1.03700	-0.18400
O	-1.67600	-1.33500	-2.19500
Ag	0.18800	0.31500	-0.37700
O	0.73300	2.37100	-0.66300
S	1.00600	3.34500	0.53600
C	2.23000	2.50900	1.57700
H	2.38200	3.12100	2.47500
H	1.85500	1.50900	1.83500
H	3.15600	2.45000	0.99500
C	-0.42300	3.19200	1.63900

H	-0.57000	2.13200	1.89200
H	-0.21600	3.79000	2.53700
H	-1.28600	3.60000	1.10200
C	-0.17100	-1.75500	0.00200
C	-0.23700	-2.09500	1.37000
C	0.53700	-2.66100	-0.82400
C	0.34900	-3.24500	1.90000
C	1.15100	-3.81000	-0.31800
H	0.57400	-2.45800	-1.89500
C	1.04900	-4.10400	1.04600
H	0.27000	-3.46000	2.96600
H	1.69300	-4.48000	-0.98500
H	1.51000	-5.00400	1.45400
C	-1.89500	-1.22400	-1.00000
Cl	-1.06400	-1.01900	2.51900

***p*-Cl TS BP**

O	-2.28900	0.33500	1.14100
O	-2.28700	0.32300	-1.17600
Ag	0.57600	0.77500	-0.01900
O	1.58400	2.67100	-0.01300
S	0.81600	4.03900	0.02300
C	-0.34400	3.92300	1.41100
H	-0.97500	4.82100	1.39600
H	-0.94800	3.01200	1.30000
H	0.25700	3.89500	2.32600
C	-0.38800	3.96900	-1.33200
H	-0.98100	3.04800	-1.23900
H	-1.02500	4.85900	-1.25900
H	0.18300	3.98400	-2.26600
C	-0.26800	-1.16000	-0.00700
C	-0.17100	-1.87600	1.20600
C	-0.17000	-1.89200	-1.21000
C	0.05400	-3.25500	1.22800
C	0.05500	-3.27200	-1.21400
H	-0.28800	-1.38200	-2.16800
C	0.16700	-3.93400	0.01200
H	0.13400	-3.82600	-2.14800
C	-1.96100	0.17000	-0.01600
H	-0.28900	-1.35400	2.15700
Cl	0.44100	-5.68000	0.02400
H	0.13300	-3.79700	2.17000

***m*-Et TS BP**

O	-2.78400	-0.76800	-0.26900
O	-1.85800	-1.18900	-2.35400
Ag	0.14100	0.31600	-0.48900
O	0.66700	2.40100	-0.59700
S	0.96300	3.23600	0.69600
C	2.22900	2.30800	1.60300
H	2.39100	2.81200	2.56500
H	1.87900	1.27600	1.74700
H	3.14100	2.33700	0.99800
C	-0.43300	2.92900	1.81200
H	-0.55800	1.84400	1.93600
H	-0.21000	3.41600	2.77100
H	-1.31600	3.38300	1.35100
C	-0.16000	-1.75100	-0.20000
C	-0.37500	-2.13600	1.13700
C	0.55800	-2.63200	-1.03900
C	0.13900	-3.33200	1.67200
C	1.07300	-3.82700	-0.53000
H	0.70600	-2.38600	-2.09200
C	0.87200	-4.17000	0.81500
H	1.63500	-4.50100	-1.18000
H	1.28500	-5.10800	1.19100
C	-2.00500	-1.01500	-1.16300
H	-0.97100	-1.49300	1.79100
C	-0.13300	-3.67700	3.12800
H	-0.02000	-2.75800	3.72400
H	-1.19600	-3.95500	3.22600
C	0.73200	-4.78700	3.73000
H	0.56700	-5.75100	3.23000
H	1.80300	-4.54800	3.65400
H	0.49100	-4.92000	4.79400

***o*-Et TS BP**

O	-2.71500	-0.85600	-0.06700
O	-1.73300	-1.22500	-2.12400
Ag	0.26000	0.27700	-0.37900
O	0.84500	2.32900	-0.65700
S	0.90300	3.35300	0.52900
C	1.91100	2.56300	1.81100
H	1.90300	3.21400	2.69500
H	1.48900	1.57400	2.04000
H	2.92600	2.47800	1.41000
C	-0.70500	3.24500	1.36100
H	-0.90700	2.19400	1.61200
H	-0.65700	3.86800	2.26400
H	-1.45300	3.63900	0.66600
C	-0.10300	-1.77900	0.02700
C	-0.16200	-2.12300	1.40900
C	0.47700	-2.69300	-0.87800
C	0.35600	-3.36300	1.81900
C	1.01400	-3.91200	-0.44900
H	0.47800	-2.45300	-1.94200
C	0.94400	-4.24700	0.90600
H	0.31000	-3.64600	2.87200
H	1.46400	-4.59900	-1.16700
H	1.34100	-5.20100	1.25700
C	-1.88100	-1.08800	-0.92200
C	-0.73000	-1.14200	2.42100
H	0.04200	-0.37900	2.61900
H	-1.56000	-0.61200	1.93400
C	-1.19400	-1.72200	3.76100
H	-0.36400	-2.16100	4.33200
H	-1.63300	-0.92900	4.38100
H	-1.95700	-2.50100	3.61900

***p*-Et TS BP**

O	-2.23300	-0.09000	1.24200
O	-2.30100	-0.07600	-1.07600
Ag	0.58200	0.53200	0.01800
O	1.47700	2.48700	0.01400
S	0.62500	3.80300	-0.04600
C	-0.57600	3.68000	1.30500
H	-1.25400	4.54000	1.22900
H	-1.12400	2.73200	1.21600
H	-0.00800	3.72600	2.24000
C	-0.51600	3.59300	-1.43900
H	-1.06900	2.65200	-1.31200
H	-1.19400	4.45600	-1.44800
H	0.09400	3.57900	-2.34900
C	-0.12200	-1.45100	0.00600
C	0.02900	-2.19200	1.19600
C	-0.01800	-2.15900	-1.21400
C	0.30900	-3.56500	1.17300
C	0.26100	-3.52500	-1.23700
H	-0.17500	-1.63500	-2.15900
C	0.43400	-4.25600	-0.04400
H	0.33900	-4.04500	-2.19600
C	-1.93700	-0.21300	0.07300
H	-0.09100	-1.69700	2.16200
H	0.42200	-4.09900	2.11700
C	0.72800	-5.74400	-0.12000
H	-0.06700	-6.22000	-0.71700
H	1.64800	-5.87900	-0.71300
C	0.87100	-6.47600	1.21500
H	-0.04800	-6.41000	1.81400
H	1.08300	-7.53900	1.04100
H	1.69400	-6.06500	1.81700

***m*-F TS BP**

O	-2.28000	-0.39400	1.12100
O	-2.28800	-0.44100	-1.19600
Ag	0.56100	0.20100	-0.05800
O	1.49100	2.13500	-0.08900
S	0.67500	3.46900	0.04500
C	-0.37400	3.26600	1.50900
H	-1.02400	4.14700	1.57900
H	-0.96300	2.34400	1.40500
H	0.29500	3.21800	2.37400

C	-0.62000	3.39100	-1.22100
H	-1.17600	2.45000	-1.11000
H	-1.27700	4.25800	-1.08000
H	-0.11900	3.44700	-2.19300
C	-0.18100	-1.78000	-0.01500
C	-0.03400	-2.45500	1.21700
C	-0.01100	-2.51700	-1.20800
C	0.30600	-3.80100	1.21000
C	0.33600	-3.87300	-1.18000
H	-0.16900	-2.02800	-2.17100
C	0.50000	-4.53400	0.04400
H	0.47000	-4.42600	-2.11000
H	0.75400	-5.59200	0.09900
C	-1.95100	-0.55800	-0.03600
H	-0.20300	-1.95000	2.16900
F	0.45200	-4.45100	2.41900

***o*-F TS BP**

O	-2.66100	-0.79300	0.22100
O	-1.94400	-1.13400	-1.95000
Ag	0.38500	0.26100	-0.37400
O	1.06100	2.28300	-0.61300
S	0.85900	3.37600	0.49500
C	1.51300	2.65400	2.02200
H	1.31700	3.36300	2.83700
H	1.01500	1.69100	2.20600
H	2.59100	2.52600	1.87800
C	-0.90200	3.33800	0.92000
H	-1.18600	2.31200	1.19100
H	-1.05600	4.02700	1.76100
H	-1.45100	3.68600	0.03800
C	-0.15900	-1.77100	-0.04100
C	-0.11600	-2.15300	1.30900
C	0.34400	-2.73200	-0.95400
C	0.37700	-3.36500	1.77500
C	0.86400	-3.95800	-0.53000
H	0.28900	-2.50900	-2.02100
C	0.87800	-4.27500	0.83600
H	0.37500	-3.58300	2.84300
H	1.24600	-4.67200	-1.26000
H	1.27100	-5.23300	1.17500
C	-1.95700	-1.04600	-0.73600
F	-0.58300	-1.26700	2.25900

***p*-F TS BP**

O	-2.28300	-0.18700	1.14500
O	-2.28100	-0.20500	-1.17300
Ag	0.57600	0.40600	-0.01100
O	1.49400	2.34700	-0.01000
S	0.65600	3.67300	0.01500
C	-0.50400	3.50100	1.39700
H	-1.17200	4.37100	1.38400
H	-1.06800	2.56500	1.28000
H	0.09400	3.49400	2.31500
C	-0.53200	3.53500	-1.34800
H	-1.08700	2.59200	-1.24600
H	-1.20500	4.40000	-1.29600
H	0.04700	3.55800	-2.27700
C	-0.16200	-1.56700	-0.00400
C	-0.03100	-2.27800	1.21100
C	-0.02600	-2.29100	-1.21000
C	0.26200	-3.64600	1.23300
C	0.26600	-3.65900	-1.21600
H	-0.16800	-1.78600	-2.16600
C	0.40700	-4.29800	0.01200
H	0.37400	-4.22400	-2.14200
C	-1.95400	-0.33300	-0.01300
H	-0.17700	-1.76200	2.16100
H	0.36600	-4.20000	2.16500
F	0.68600	-5.64500	0.02000

***m*-NH_2 TS BP**

O	-2.57000	-0.44800	0.29200
O	-2.07300	-0.90300	-1.92600
Ag	0.37600	0.24400	-0.40800
O	1.10600	2.25600	-0.61700

S	0.78700	3.37200	0.43800
C	1.24500	2.67300	2.04600
H	0.94600	3.39000	2.82200
H	0.73100	1.71000	2.17500
H	2.33300	2.54700	2.04000
C	-1.01300	3.36200	0.64900
H	-1.34100	2.34300	0.89800
H	-1.25800	4.06800	1.45300
H	-1.44600	3.70000	-0.29900
C	-0.14000	-1.77900	-0.10000
C	-0.21100	-2.18700	1.24500
C	0.32100	-2.69800	-1.06700
C	0.20500	-3.47100	1.65100
C	0.73400	-3.97800	-0.67300
H	0.33900	-2.42500	-2.12300
C	0.68300	-4.36400	0.67000
H	1.09200	-4.69000	-1.41900
H	0.99800	-5.36700	0.96600
C	-1.98400	-0.76200	-0.72300
H	-0.61900	-1.50900	2.00000
N	0.20100	-3.83300	3.00800
H	-0.48600	-3.32900	3.56600
H	0.11800	-4.83600	3.16600

***o*-NH_2 TS BP**

O	-2.74400	-0.95300	-0.23000
O	-1.67300	-1.40900	-2.23800
Ag	0.17600	0.32500	-0.37200
O	0.56100	2.42500	-0.65700
S	0.96400	3.36200	0.53400
C	2.36700	2.54700	1.34200
H	2.60700	3.11300	2.25200
H	2.08600	1.51200	1.58100
H	3.20400	2.58200	0.63800
C	-0.27600	3.08900	1.82900
H	-0.32500	2.01600	2.06200
H	0.02700	3.67300	2.70800
H	-1.23000	3.45900	1.43800
C	-0.04000	-1.72800	0.04300
C	-0.31500	-2.10600	1.39100
C	0.71200	-2.62400	-0.75000
C	0.20500	-3.31600	1.90300
C	1.23300	-3.81600	-0.24100
H	0.88100	-2.37900	-1.80100
C	0.97800	-4.15200	1.09900
H	-0.00800	-3.59300	2.93800
H	1.82200	-4.48000	-0.87500
H	1.37000	-5.08100	1.51600
C	-1.90900	-1.20000	-1.07200
N	-1.05500	-1.26200	2.22300
H	-1.74100	-0.71100	1.70600
H	-1.48800	-1.73300	3.01700

***p*-NH_2 TS BP**

O	-2.29300	0.25600	1.27000
O	-2.35300	0.30600	-1.05100
Ag	0.61500	0.79200	0.05200
O	1.58100	2.71800	0.06600
S	0.78700	4.06300	-0.06900
C	-0.50100	4.01200	1.20600
H	-1.14200	4.89300	1.07100
H	-1.07400	3.08100	1.10200
H	0.01000	4.05900	2.17400
C	-0.27700	3.86700	-1.52400
H	-0.86500	2.94500	-1.41700
H	-0.92800	4.74800	-1.58600
H	0.38300	3.82000	-2.39700
C	-0.16900	-1.14700	0.02200
C	-0.08500	-1.92400	1.20300
C	-0.14200	-1.85900	-1.20300
C	0.05500	-3.31100	1.17100
C	-0.00200	-3.24500	-1.25400
H	-0.25000	-1.31700	-2.14500
C	0.10500	-3.99700	-0.06300
H	0.01600	-3.76100	-2.21700
C	-2.01900	0.14700	0.09900

H	-0.14900	-1.43500	2.17700
H	0.11700	-3.88000	2.10300
N	0.30000	-5.37500	-0.10600
H	0.01700	-5.87900	0.73200
H	-0.03400	-5.83400	-0.95000

_m_-NO_2 TS BP

O	-2.58200	-0.48400	0.35700
O	-2.11500	-0.93200	-1.86800
Ag	0.37600	0.25200	-0.38200
O	1.19600	2.22200	-0.57100
S	1.89900	2.94900	0.62900
C	3.13500	1.78000	1.25000
H	3.58100	2.21000	2.15600
H	2.64100	0.82200	1.46800
H	3.89200	1.66900	0.46700
C	0.73100	2.86000	2.01100
H	0.45100	1.81000	2.17700
H	1.22500	3.28300	2.89500
H	-0.13700	3.46700	1.73400
C	-0.21900	-1.76600	-0.09600
C	-0.24600	-2.18300	1.24800
C	0.26900	-2.67600	-1.06000
C	0.24500	-3.44500	1.59300
C	0.76000	-3.93700	-0.69900
H	0.25300	-2.39800	-2.11500
C	0.75600	-4.33300	0.63900
H	1.14000	-4.61800	-1.46000
H	1.12200	-5.31000	0.94500
C	-2.01200	-0.80900	-0.66400
H	-0.66500	-1.54600	2.02600
N	0.21400	-3.86000	3.00000
O	0.66800	-4.98300	3.29600
O	-0.26100	-3.07200	3.84000

_o_-NO_2 TS BP

O	-2.58800	0.15400	1.47300
O	-2.48800	0.76100	-0.75500
Ag	0.38100	1.10200	0.38300
O	1.37900	3.00700	0.43600
S	0.90300	4.22900	-0.42600
C	-0.85700	4.44200	-0.05100
H	-1.24300	5.23700	-0.70300
H	-1.38100	3.49300	-0.23000
H	-0.92400	4.74800	0.99900
C	0.73800	3.60400	-2.11900
H	0.08900	2.71600	-2.10800
H	0.30400	4.40400	-2.73300
H	1.74600	3.35900	-2.46800
C	-0.50200	-0.83300	0.09900
C	-0.17800	-1.78000	1.09700
C	-0.47400	-1.32100	-1.22300
C	0.14500	-3.11100	0.83400
C	-0.10600	-2.63800	-1.52500
H	-0.79000	-0.65600	-2.02800
C	0.19700	-3.53500	-0.49600
H	-0.07400	-2.96900	-2.56400
C	-2.19300	0.29600	0.33200
H	0.38200	-3.78800	1.65200
H	0.47200	-4.56500	-0.72400
N	-0.15800	-1.36700	2.51200
O	-0.43000	-2.22000	3.37700
O	0.13800	-0.18700	2.79200

***p*-NO_2 TS BP**

O	-2.33700	0.55000	1.15800
O	-2.33700	0.55000	-1.15800
Ag	0.51600	0.96600	0.00000
O	1.56800	2.83200	0.00000
S	0.82200	4.21400	0.00000
C	-0.35900	4.13900	1.37200
H	-0.96400	5.05500	1.34300
H	-0.98900	3.24600	1.26000
H	0.22800	4.10100	2.29600
C	-0.35900	4.13900	-1.37200
H	-0.98900	3.24600	-1.26000

H	-0.96400	5.05500	-1.34300
H	0.22800	4.10100	-2.29600
C	-0.38900	-0.95400	0.00000
C	-0.26900	-1.66800	1.21300
C	-0.26900	-1.66800	-1.21300
C	0.01500	-3.03200	1.22600
C	0.01500	-3.03200	-1.22600
H	-0.41300	-1.15200	-2.16300
C	0.15800	-3.69200	0.00000
H	0.12000	-3.58400	-2.15700
C	-2.00600	0.37800	0.00000
H	-0.41300	-1.15200	2.16300
H	0.12000	-3.58400	2.15700
N	0.45700	-5.12700	0.00000
O	0.57800	-5.70700	-1.09700
O	0.57800	-5.70700	1.09700

***m*-OMe TS BP**

O	-1.76000	-0.03700	1.35500
O	-2.28200	-0.22200	-0.89600
Ag	0.79200	0.01000	-0.42400
O	1.97400	1.77200	-0.76600
S	2.42700	2.71000	0.40600
C	3.21200	1.62500	1.62800
H	3.46700	2.23600	2.50400
H	2.51200	0.82100	1.89500
H	4.12000	1.22800	1.16300
C	0.92400	3.10800	1.33700
H	0.41900	2.17600	1.62400
H	1.22300	3.68600	2.22200
H	0.29500	3.71800	0.68000
C	-0.17100	-1.83600	-0.06100
C	0.14900	-2.43600	1.16800
C	-0.38500	-2.66700	-1.18500
C	0.29500	-3.83000	1.27800
C	-0.24200	-4.05200	-1.07200
H	-0.68100	-2.23100	-2.14000
C	0.10100	-4.64500	0.15200
H	-0.40500	-4.69100	-1.94100
H	0.19800	-5.72700	0.22000
C	-1.71800	-0.31400	0.17500
H	0.26900	-1.83400	2.07100
O	0.62400	-4.30200	2.53100
C	0.79500	-5.72900	2.67000
H	1.60100	-6.09300	2.01900
H	-0.13800	-6.26100	2.43900
H	1.06400	-5.89200	3.71700

***o*-OMe TS BP**

O	-2.67800	-0.90500	-0.00000
O	-1.77800	-1.22700	-2.10600
Ag	0.29800	0.27800	-0.41700
O	0.82400	2.35800	-0.62200
S	0.84200	3.30800	0.62500
C	1.88500	2.48000	1.85500
H	1.85800	3.07500	2.77600
H	1.49800	1.46400	2.02200
H	2.90100	2.45700	1.44600
C	-0.75800	3.08300	1.44800
H	-0.92100	2.00900	1.62100
H	-0.72900	3.64100	2.39300
H	-1.52200	3.50100	0.78500
C	-0.08000	-1.77100	-0.02800
C	-0.11500	-2.07700	1.36300
C	0.44000	-2.75600	-0.89200
C	0.33900	-3.31600	1.84400
C	0.92100	-3.98300	-0.42200
H	0.43500	-2.55800	-1.96500
C	0.86000	-4.25800	0.94800
H	0.30600	-3.54800	2.90800
H	1.32100	-4.72300	-1.11700
H	1.21700	-5.21400	1.33300
C	-1.88800	-1.11800	-0.89700
O	-0.59000	-1.08700	2.18500
C	-0.68100	-1.37200	3.59600
H	0.31100	-1.56700	4.02500

H	-1.10800	-0.47400	4.04900
H	-1.34200	-2.22900	3.78500

***p*-OMe TS BP**

O	-2.10200	0.05100	1.18300
O	-2.26200	-0.10000	-1.12700
Ag	0.73500	0.49300	-0.17300
O	1.71000	2.40800	-0.28300
S	0.93000	3.75400	-0.08200
C	-0.00300	3.56200	1.46100
H	-0.63100	4.45400	1.58500
H	-0.61200	2.64900	1.40200
H	0.73300	3.50000	2.27000
C	-0.46300	3.69600	-1.24100
H	-1.02100	2.76300	-1.08200
H	-1.09300	4.57400	-1.05300
H	-0.03900	3.73900	-2.25000
C	-0.05900	-1.44400	-0.03300
C	0.09400	-2.11100	1.20100
C	-0.04200	-2.24700	-1.20100
C	0.29300	-3.49400	1.28500
C	0.15400	-3.62300	-1.14300
H	-0.20200	-1.78600	-2.17700
C	0.32900	-4.25400	0.10400
H	0.16700	-4.23100	-2.04900
C	-1.87000	-0.16500	0.01500
H	0.04000	-1.54400	2.13200
H	0.40800	-3.96600	2.25900
O	0.51100	-5.61400	0.06600
C	0.68200	-6.29100	1.33200
H	0.81600	-7.34700	1.08300
H	1.57000	-5.91700	1.85800
H	-0.20700	-6.16700	1.96400

***m*-OEt TS BP**

O	-1.78900	-0.03900	1.33200
O	-2.28700	-0.23600	-0.92300
Ag	0.77800	0.01800	-0.42500
O	1.96100	1.78100	-0.76400
S	2.44300	2.69500	0.41600
C	3.23600	1.58300	1.60800
H	3.51300	2.17700	2.48900
H	2.53100	0.78300	1.87400
H	4.13100	1.18200	1.12100
C	0.95800	3.09300	1.37600
H	0.44600	2.16000	1.65100
H	1.27500	3.65000	2.26700
H	0.32700	3.72200	0.73900
C	-0.17700	-1.83300	-0.06300
C	0.14300	-2.42900	1.16900
C	-0.38200	-2.66900	-1.18500
C	0.30200	-3.82100	1.28500
C	-0.23000	-4.05200	-1.06700
H	-0.67700	-2.23800	-2.14200
C	0.11500	-4.64000	0.16000
H	-0.38600	-4.69500	-1.93500
H	0.21700	-5.72100	0.23100
C	-1.73300	-0.32200	0.15400
H	0.25400	-1.82300	2.07100
O	0.63300	-4.28500	2.53800
C	0.82900	-5.71800	2.69200
H	1.61200	-6.04900	1.99300
H	-0.10700	-6.23700	2.43800
C	1.23200	-5.97600	4.12900
H	1.38600	-7.05400	4.27400
H	2.16900	-5.45800	4.37500
H	0.44900	-5.64300	4.82400

***o*-OEt TS BP**

O	-2.68800	-0.90100	-0.05100
O	-1.74600	-1.18900	-2.14400
Ag	0.33600	0.26100	-0.38700
O	0.92700	2.32500	-0.57900
S	0.77000	3.31200	0.63000
C	1.57400	2.49300	2.03200
H	1.39400	3.10100	2.92800

H	1.15200	1.48300	2.14000
H	2.64500	2.45300	1.80700
C	-0.94900	3.14600	1.18200
H	-1.16200	2.08300	1.36500
H	-1.06700	3.74400	2.09500
H	-1.58000	3.54700	0.38100
C	-0.10000	-1.78400	-0.04500
C	-0.16000	-2.13000	1.33600
C	0.43300	-2.74800	-0.92800
C	0.28000	-3.38700	1.78600
C	0.90000	-3.99100	-0.48800
H	0.44600	-2.51900	-1.99500
C	0.81200	-4.30500	0.87300
H	0.22600	-3.65200	2.84100
H	1.30900	-4.71200	-1.19600
H	1.15400	-5.27500	1.23600
C	-1.88300	-1.10700	-0.93500
O	-0.64400	-1.16600	2.18100
C	-0.76600	-1.49600	3.59100
H	0.23000	-1.73600	3.99300
H	-1.40700	-2.38400	3.70000
C	-1.36800	-0.29900	4.29900
H	-2.35700	-0.05500	3.88900
H	-1.48200	-0.52900	5.36700
H	-0.72000	0.58400	4.20800

***p*-OEt TS BP**

O	-2.14400	0.03400	1.42600
O	-2.47500	-0.02300	-0.87400
Ag	0.56100	0.52300	-0.14500
O	1.58900	2.41400	-0.28100
S	3.09400	2.54100	0.14100
C	3.97000	1.23900	-0.76600
H	5.00700	1.21600	-0.40600
H	3.46500	0.28000	-0.58500
H	3.94000	1.51300	-1.82600
C	3.20200	1.81900	1.80000
H	2.78500	0.80200	1.77400
H	4.26000	1.80700	2.09300
H	2.62900	2.47100	2.46700
C	-0.18300	-1.43200	0.00100
C	0.09300	-2.12700	1.19700
C	-0.24400	-2.20200	-1.18600
C	0.35000	-3.50300	1.22200
C	0.00800	-3.57200	-1.18600
H	-0.49900	-1.72200	-2.13300
C	0.32300	-4.22900	0.01900
H	-0.03200	-4.15300	-2.10900
C	-2.00900	-0.12300	0.23600
H	0.10100	-1.58800	2.14700
H	0.56400	-3.99600	2.16800
O	0.57700	-5.57500	-0.08000
C	0.95800	-6.27700	1.13700
H	1.83600	-5.78000	1.57500
H	0.12800	-6.22000	1.85700
C	1.26700	-7.71100	0.76400
H	1.55900	-8.26600	1.66600
H	0.38900	-8.20400	0.32500
H	2.09800	-7.76000	0.04600

***m*-OH TS BP**

O	-2.27900	-0.41300	1.17700
O	-2.30300	-0.40000	-1.14100
Ag	0.55700	0.20100	-0.01200
O	1.49100	2.13500	-0.00600
S	0.67800	3.47700	0.00600
C	-0.50200	3.33600	1.37500
H	-1.14900	4.22300	1.34800
H	-1.08800	2.41500	1.25500
H	0.08400	3.32100	2.30000
C	-0.49800	3.35800	-1.36800
H	-1.07400	2.42800	-1.27000
H	-1.15400	4.23700	-1.32500
H	0.09100	3.36800	-2.29100
C	-0.17000	-1.78300	-0.00900
C	-0.00800	-2.48200	1.20500

C	-0.02800	-2.49500	-1.22000
C	0.32300	-3.84300	1.20700
C	0.30100	-3.85500	-1.21000
H	-0.19600	-1.98900	-2.17300
C	0.48100	-4.53600	-0.00200
H	0.41200	-4.39900	-2.15000
H	0.72700	-5.59800	0.01800
C	-1.95900	-0.54300	0.01400
H	-0.16100	-1.97400	2.16100
O	0.49700	-4.55800	2.37800
H	0.36100	-3.94800	3.13000

_o_-OH TS BP

O	-2.52200	-0.54500	0.42200
O	-2.09400	-1.03300	-1.81100
Ag	0.41000	0.24200	-0.34300
O	1.05100	2.26700	-0.64900
S	0.81900	3.41000	0.40000
C	1.42900	2.76200	1.97900
H	1.18400	3.49500	2.75900
H	0.94800	1.79400	2.17800
H	2.51400	2.65600	1.88200
C	-0.95400	3.39100	0.77800
H	-1.24500	2.38100	1.09800
H	-1.13200	4.12400	1.57500
H	-1.47800	3.68800	-0.13600
C	-0.01800	-1.79300	-0.01100
C	-0.15100	-2.26600	1.31700
C	0.50600	-2.69500	-0.96600
C	0.30500	-3.53800	1.69500
C	0.96200	-3.96600	-0.60400
H	0.56400	-2.38800	-2.01200
C	0.87500	-4.37700	0.73500
H	0.19300	-3.85900	2.73200
H	1.38200	-4.63400	-1.35700
H	1.23000	-5.36500	1.03000
C	-1.99300	-0.86400	-0.62600
O	-0.74100	-1.48700	2.29300
H	-1.34800	-0.87400	1.80700

***p*-OH TS BP**

O	-2.26600	0.14300	1.49800
O	-2.40500	0.39100	-0.80500
Ag	0.56600	0.79600	0.20300
O	1.54000	2.71500	0.26200
S	0.84100	4.02400	-0.24400
C	-0.70600	4.15800	0.69300
H	-1.26700	5.01200	0.29100
H	-1.27300	3.22400	0.58600
H	-0.43100	4.34100	1.73700
C	0.13200	3.61400	-1.86100
H	-0.50300	2.72200	-1.75700
H	-0.45100	4.47800	-2.20300
H	0.97300	3.43000	-2.53900
C	-0.22200	-1.14500	0.06600
C	-0.06000	-1.99900	1.18100
C	-0.21800	-1.75000	-1.21300
C	0.13400	-3.37400	1.03400
C	-0.02400	-3.12200	-1.38200
H	-0.38700	-1.13900	-2.10100
C	0.15800	-3.93400	-0.25300
H	-0.02100	-3.57600	-2.37400
C	-2.02200	0.13000	0.31300
H	-0.10300	-1.58700	2.19100
H	0.25800	-4.01900	1.90700
O	0.33800	-5.28300	-0.46100
H	0.44100	-5.71700	0.40900

***m*-O^{i}Pr TS BP**

O	-2.06100	-0.12500	1.21500
O	-2.46800	-0.28700	-1.06500
Ag	0.57900	0.09700	-0.44500
O	1.77100	1.88100	-0.65600
S	3.25300	1.91500	-0.14600
C	4.07500	0.50600	-0.93800
H	5.08600	0.42500	-0.51900

H	3.48700	-0.40200	-0.74200
H	4.12100	0.72500	-2.00900
C	3.20800	1.26900	1.54700
H	2.70100	0.29300	1.54100
H	4.24200	1.17700	1.90200
H	2.65900	1.99700	2.15400
C	-0.27800	-1.80800	-0.17000
C	0.05400	-2.40800	1.05600
C	-0.40900	-2.63300	-1.30900
C	0.30400	-3.79000	1.16200
C	-0.17100	-4.00600	-1.20800
H	-0.70600	-2.20500	-2.26800
C	0.18800	-4.59300	0.01400
H	-0.26900	-4.64400	-2.08800
H	0.35700	-5.66500	0.05700
C	-1.96200	-0.36200	0.03200
H	0.11800	-1.81200	1.97000
O	0.61900	-4.21500	2.43400
C	1.12500	-5.56500	2.73600
H	1.35800	-5.44800	3.80300
C	2.42900	-5.88100	2.01000
H	2.87100	-6.78200	2.45700
H	2.28800	-6.07200	0.93900
H	3.14500	-5.05600	2.13100
C	0.04600	-6.63800	2.61800
H	0.40400	-7.55200	3.11400
H	-0.87300	-6.31500	3.12400
H	-0.19600	-6.89600	1.57900

***o*-O^{i}Pr TS BP**

O	-2.59900	-0.81500	0.16400
O	-1.90100	-1.14200	-2.01500
Ag	0.38700	0.24500	-0.46000
O	0.93100	2.33700	-0.53500
S	0.70500	3.22800	0.73600
C	1.51900	2.34700	2.09800
H	1.30400	2.89200	3.02700
H	1.12900	1.32000	2.13200
H	2.59400	2.36100	1.88900
C	-1.01400	2.94600	1.24300
H	-1.18400	1.86300	1.33500
H	-1.16900	3.45900	2.20000
H	-1.65200	3.38600	0.46900
C	-0.06300	-1.79700	-0.10300
C	-0.00600	-2.12400	1.28600
C	0.32800	-2.79000	-1.02600
C	0.39900	-3.40700	1.69800
C	0.76100	-4.05600	-0.62200
H	0.24900	-2.56300	-2.09100
C	0.78300	-4.35700	0.74500
H	0.43900	-3.67200	2.75100
H	1.05900	-4.80200	-1.35900
H	1.10200	-5.34400	1.08400
C	-1.89900	-1.05200	-0.79900
O	-0.32700	-1.09300	2.12900
C	-0.50800	-1.23500	3.58400
H	-0.85000	-0.22000	3.83000
C	0.80800	-1.46400	4.32400
H	1.57900	-0.76700	3.96800
H	0.64800	-1.27200	5.39500
H	1.19000	-2.48700	4.22100
C	-1.63200	-2.19600	3.95500
H	-1.36500	-3.25000	3.80300
H	-1.87000	-2.06200	5.02000
H	-2.53400	-1.97100	3.37200

***p*-O^{i}Pr TS BP**

O	-1.97000	0.16100	1.53900
O	-2.50200	0.03000	-0.72000
Ag	0.61600	0.52000	-0.28100
O	1.65800	2.38800	-0.56300
S	3.03200	2.65900	0.14300
C	4.06900	1.22100	-0.23400
H	5.00600	1.32400	0.32900
H	3.52900	0.30800	0.05500
H	4.26600	1.24400	-1.31100

C	2.75600	2.32500	1.90400
H	2.33100	1.31800	2.01300
H	3.72400	2.40600	2.41600
H	2.06600	3.09300	2.26900
C	-0.16900	-1.40100	0.00500
C	0.19200	-2.05800	1.20100
C	-0.36300	-2.22200	-1.13200
C	0.40000	-3.44000	1.26900
C	-0.16300	-3.59900	-1.08600
H	-0.68500	-1.77700	-2.07500
C	0.23600	-4.22600	0.11400
H	-0.30900	-4.21800	-1.97300
C	-1.94400	-0.04400	0.34900
H	0.30700	-1.48300	2.12200
H	0.68400	-3.88500	2.21900
O	0.40300	-5.58400	0.01600
C	0.89200	-6.42700	1.12300
H	0.92600	-7.40200	0.61800
C	2.31500	-6.07600	1.54600
H	2.69600	-6.88000	2.19100
H	2.97100	-6.00800	0.66700
H	2.37800	-5.13700	2.10700
C	-0.11300	-6.53700	2.26600
H	-0.16700	-5.63000	2.88000
H	-1.11500	-6.76000	1.87600
H	0.18900	-7.36700	2.92000

H TS BP

O	-2.24600	-0.42200	1.15900
O	-2.24600	-0.42200	-1.15900
Ag	0.57300	0.21100	0.00000
O	1.47100	2.16400	0.00000
S	0.63500	3.49100	0.00000
C	-0.54000	3.34100	1.37200
H	-1.21200	4.20900	1.33300
H	-1.09900	2.40100	1.26700
H	0.04600	3.35600	2.29700
C	-0.54000	3.34100	-1.37200
H	-1.09900	2.40100	-1.26700
H	-1.21200	4.20900	-1.33300
H	0.04600	3.35600	-2.29700
C	-0.11400	-1.78400	0.00000
C	0.03400	-2.49600	1.21100
C	0.03400	-2.49600	-1.21100
C	0.36000	-3.85800	1.21300
H	-0.12500	-1.98400	2.16200
C	0.36000	-3.85800	-1.21300
H	-0.12500	-1.98400	-2.16200
C	0.52800	-4.53900	0.00000
H	0.47500	-4.39000	2.15900
H	0.47500	-4.39000	-2.15900
H	0.77300	-5.60200	0.00000
C	-1.90800	-0.55200	0.00000

***o*-Br+*m*-NO_2 TS BP**

O	-1.97100	-1.02100	-1.13600
O	0.14000	-0.91600	-2.06600
Ag	0.34800	0.39900	0.70600
O	0.80300	2.47700	0.96500
S	1.25800	3.37900	-0.23700
C	0.01300	3.14300	-1.53300
H	0.35100	3.68800	-2.42400
H	-0.08500	2.06900	-1.74200
H	-0.92300	3.56800	-1.15800
C	2.62900	2.49600	-1.02700
H	2.30000	1.48000	-1.28800
H	2.91800	3.05800	-1.92400
H	3.45300	2.47900	-0.30600
C	0.04900	-1.71300	0.46700
C	-0.75500	-2.30400	1.46900
C	1.23200	-2.40200	0.13200
C	-0.43000	-3.51200	2.09700
C	1.57400	-3.59100	0.77500
H	1.86600	-2.02300	-0.66600
C	0.75000	-4.16600	1.74800
H	-1.08100	-3.93500	2.86000

H	1.02700	-5.10600	2.21900
C	-0.76000	-1.04500	-1.25100
Br	-2.34900	-1.41600	2.07200
N	2.81600	-4.27000	0.40300
O	3.54300	-3.74300	-0.46200
O	3.09300	-5.34700	0.96800

***o*-Cl+*m*-NO_2 TS BP**

O	-1.47500	-0.74900	-1.39100
O	0.73800	-0.89900	-2.03100
Ag	0.72800	0.31600	0.80700
O	1.30100	2.33500	1.24100
S	1.31200	3.44700	0.13100
C	-0.34300	3.42100	-0.60600
H	-0.34500	4.11700	-1.45400
H	-0.57600	2.39800	-0.93300
H	-1.04000	3.76200	0.16800
C	2.23600	2.74600	-1.26000
H	1.80200	1.77100	-1.52600
H	2.16400	3.45100	-2.09900
H	3.27600	2.64800	-0.93300
C	0.20400	-1.73100	0.42600
C	-0.80500	-2.23200	1.28300
C	1.32200	-2.56700	0.23300
C	-0.73100	-3.48300	1.90500
C	1.41200	-3.80400	0.87100
H	2.10700	-2.25800	-0.45500
C	0.39000	-4.28100	1.70000
H	-1.53700	-3.82200	2.55200
H	0.47400	-5.25700	2.17000
C	-0.27200	-0.93200	-1.34500
N	2.59200	-4.63900	0.64800
O	3.49700	-4.20000	-0.08900
O	2.64100	-5.75200	1.20600
Cl	-2.22100	-1.25200	1.64100

***o*-F+*m*-NO_2 TS BP**

O	-1.43000	-0.74600	-1.43900
O	0.78300	-0.88800	-2.08700
Ag	0.77000	0.32800	0.78500
O	1.31300	2.35100	1.23300
S	1.26300	3.48300	0.14400
C	-0.42100	3.45300	-0.52300
H	-0.46300	4.16900	-1.35400
H	-0.65900	2.43700	-0.86800
H	-1.08900	3.77000	0.28500
C	2.13300	2.81600	-1.29800
H	1.69400	1.84400	-1.56400
H	2.02500	3.53600	-2.11900
H	3.18600	2.71600	-1.01200
C	0.25100	-1.70800	0.36700
C	-0.79100	-2.20300	1.17400
C	1.36100	-2.56600	0.22800
C	-0.78600	-3.43800	1.81700
C	1.39600	-3.80100	0.87800
H	2.18200	-2.28200	-0.42800
C	0.33000	-4.25300	1.67000
H	-1.63800	-3.74300	2.42300
H	0.38000	-5.22600	2.15100
C	-0.22700	-0.92700	-1.40300
N	2.56200	-4.66600	0.70700
O	3.50500	-4.25800	0.00000
O	2.56300	-5.77600	1.27600
F	-1.89500	-1.42200	1.35500

A.2. M06 GEOMETRIES OF STATIONARY POINTS

A.2.1. Cartesian geometries of CP3 compounds at M06 level of computation.

***o*-Br CP3 M06**

O	-0.61585	-0.38058	0.81734
O	-0.21090	1.12286	-0.77814
Ag	1.61125	-0.22971	0.03950
O	3.72795	-0.87364	0.01860
S	4.79042	0.10407	-0.52850
C	6.28081	-0.33371	0.37772
H	7.07069	0.38708	0.13741
H	6.06072	-0.32488	1.45180
H	6.58961	-1.33501	0.06105
C	4.48063	1.67497	0.29628
H	4.39931	1.50151	1.37674
H	5.30251	2.36644	0.07452
H	3.54266	2.08646	-0.09580
C	-2.42702	0.92333	0.00923
C	-2.71315	2.29291	0.01032
C	-3.50652	0.03688	0.02181
C	-4.01845	2.76395	0.05799
H	-1.87718	2.98985	-0.02027
C	-4.82053	0.49393	0.04409
C	-5.07680	1.85993	0.07458
H	-4.21041	3.83525	0.07305
H	-5.64099	-0.22052	0.03402
H	-6.10640	2.21204	0.10218
C	-0.97887	0.51243	0.00973
Br	-3.25818	-1.84754	-0.07051

***o*-CF_3 CP3 M06**

O	-0.01826	-0.59389	-0.81878
O	-1.55242	-0.30275	0.78149
Ag	-0.68831	1.68942	0.23606
O	-0.10903	3.79753	-0.02426
S	-0.98284	4.88560	0.64155
C	-1.31063	6.06186	-0.67842
H	-1.82205	6.93632	-0.25919
H	-0.36253	6.35355	-1.14567
H	-1.96121	5.57264	-1.41060
C	0.18474	5.88968	1.56985
H	1.01213	6.17973	0.91147
H	-0.33375	6.77553	1.95469
H	0.55627	5.28887	2.40622
C	-1.21302	-2.48685	-0.03106
C	-2.55300	-2.84190	-0.19085
C	-0.25622	-3.50683	0.07767
C	-2.93701	-4.17446	-0.28472
H	-3.29805	-2.05033	-0.25105
C	-0.64572	-4.84355	0.00188
C	-1.98052	-5.17955	-0.19098
H	-3.98663	-4.42755	-0.42467
H	0.09957	-5.62936	0.10033
H	-2.27082	-6.22632	-0.25522
C	-0.87742	-1.01696	-0.02296
C	1.19795	-3.19970	0.28554
F	1.85736	-4.25206	0.79841
F	1.82784	-2.88473	-0.85347
F	1.38968	-2.18376	1.13951

***o*-CH_3 CP3 M06**

O	-0.70852	1.08061	0.14215
O	1.43350	0.78687	-0.39456
Ag	0.38865	-1.19520	-0.30276
O	-0.16383	-3.32669	-0.31731
S	-1.63070	-3.72162	-0.03254
C	-1.51984	-4.92545	1.29949
H	-2.50951	-5.36758	1.46434
H	-0.79095	-5.69710	1.02462
H	-1.19646	-4.39992	2.20377
C	-2.03898	-4.87040	-1.35368
H	-1.26890	-5.64957	-1.40081
H	-3.02374	-5.30979	-1.15593
H	-2.06958	-4.30666	-2.29163
C	0.70295	3.00071	0.00382
C	2.01536	3.41225	0.25915
C	-0.31281	3.96786	-0.14050
C	2.34299	4.75490	0.39601
H	2.78323	2.64694	0.35284

C	0.04136	5.31595	-0.01998
C	1.34538	5.71405	0.25330
H	3.36995	5.04996	0.60659
H	-0.73542	6.07180	-0.14381
H	1.58082	6.77344	0.34853
C	0.43817	1.52185	-0.09110
C	-1.74421	3.62959	-0.43563
H	-1.83703	2.92548	-1.27099
H	-2.23053	3.14663	0.42040
H	-2.30616	4.53940	-0.68368

***o*-Cl+*o*-Me CP3 M06**

O	-0.92503	-0.03953	-1.46026
O	-0.61692	0.05416	0.75423
Ag	1.38871	-0.09872	-0.20943
O	3.51616	-0.17179	-0.75918
S	4.49655	-0.35063	0.42504
C	4.43390	1.19845	1.33727
H	5.21500	1.19336	2.10675
H	4.57881	2.03336	0.64109
H	3.45027	1.26905	1.81646
C	6.10997	-0.11348	-0.32954
H	6.10489	0.82558	-0.89528
H	6.87228	-0.08910	0.45774
H	6.29857	-0.95916	-0.99833
C	-2.81630	0.23671	-0.05840
C	-3.66285	-0.84197	0.17045
C	-3.36209	1.53183	-0.06807
C	-5.02759	-0.68895	0.38745
C	-4.72979	1.69145	0.14999
C	-5.55760	0.59522	0.37641
H	-5.65599	-1.55937	0.56381
H	-5.15060	2.69692	0.14247
H	-6.62313	0.73978	0.54582
C	-1.33731	0.05665	-0.29086
C	-2.47410	2.71652	-0.30270
H	-1.71603	2.81036	0.48769
H	-1.93189	2.62664	-1.25384
H	-3.05357	3.64675	-0.32620
Cl	-2.99139	-2.47184	0.19084

***o*-NO_2+*o*-Me CP3 M06**

O	-0.54124	-0.15466	-0.96454
O	-0.76533	-0.18990	1.25756
Ag	1.44268	-0.06652	0.38476
O	3.63937	-0.02042	0.63160
S	4.53008	-0.03136	-0.63093
C	5.90033	-1.10805	-0.18998
H	6.65934	-1.06344	-0.97971
H	6.31768	-0.78001	0.76943
H	5.51337	-2.12869	-0.10700
C	5.42614	1.52720	-0.57693
H	5.88082	1.64881	0.41367
H	6.19437	1.52224	-1.35906
H	4.71162	2.33438	-0.76823
C	-2.71228	-0.37991	-0.06263
C	-3.18169	-1.70317	-0.14729
C	-3.64913	0.65379	-0.12175
C	-4.54933	-1.93100	-0.28621
C	-5.01706	0.42336	-0.26044
C	-5.46559	-0.88192	-0.34379
H	-4.90401	-2.95965	-0.34989
H	-5.70242	1.26449	-0.29936
H	-6.52831	-1.08669	-0.45307
C	-1.22283	-0.18818	0.08809
N	-3.21049	2.04577	-0.03132
O	-4.06413	2.92339	-0.05880
O	-2.01211	2.26942	0.06862
C	-2.21788	-2.84916	-0.08440
H	-1.47016	-2.78409	-0.88625
H	-1.66502	-2.85074	0.86501
H	-2.73765	-3.80918	-0.17855

***o*-CN CP3 M06**

O	-0.48904	1.09780	-0.07121
O	1.64423	0.46696	0.13421

Ag	0.39212	-1.38011	0.07834
O	-0.48504	-3.40042	0.08296
S	-1.94697	-3.58398	-0.38525
C	-2.68962	-4.60828	0.89176
H	-3.69177	-4.91409	0.56936
H	-2.05273	-5.48435	1.06220
H	-2.76320	-4.00838	1.80453
C	-1.85130	-4.83812	-1.67038
H	-1.29812	-5.70398	-1.28742
H	-2.86725	-5.12616	-1.96514
H	-1.32991	-4.40115	-2.52823
C	1.17787	2.77891	0.01590
C	2.53648	3.08548	0.02803
C	0.25380	3.83928	-0.01258
C	2.97846	4.40400	0.00987
H	3.24704	2.26277	0.05087
C	0.69903	5.16780	-0.02424
C	2.05842	5.44807	-0.01491
H	4.04582	4.61737	0.01614
H	-0.03223	5.97381	-0.04110
H	2.39679	6.48204	-0.02668
C	0.72927	1.34200	0.02641
C	-1.16820	3.65896	-0.02211
N	-2.33204	3.69086	-0.02714

***o*-CHO CP3 M06**

O	0.96932	0.78635	0.49292
O	0.65755	-1.07550	-0.69178
Ag	-1.27164	0.17674	-0.19256
O	-3.39357	0.79607	-0.22900
S	-4.46871	-0.31146	-0.29712
C	-5.97655	0.52929	0.20448
H	-6.78183	-0.20830	0.30029
H	-5.80248	1.04085	1.15849
H	-6.23293	1.25405	-0.57448
C	-4.24375	-1.29591	1.19144
H	-4.20172	-0.63084	2.06273
H	-5.07393	-2.00623	1.28449
H	-3.30192	-1.84818	1.08888
C	2.87379	-0.51280	-0.06807
C	3.31023	-1.83723	-0.08858
C	4.66090	-2.14485	0.03708
H	2.56867	-2.62721	-0.19055
C	5.17962	0.19754	0.17850
C	5.60025	-1.12516	0.17544
H	4.98172	-3.18529	0.02808
C	1.39451	-0.24152	-0.09827
H	6.65816	-1.36308	0.27200
C	3.82457	0.51725	0.05450
C	3.46862	1.95297	-0.03360
H	2.49310	2.17943	-0.50472
O	4.20522	2.84588	0.34028
H	5.89818	1.01148	0.26247

***o*-Cl CP3 M06**

O	-0.94602	0.68476	-0.86414
O	-0.78309	-1.01314	0.58453
Ag	1.28087	-0.53000	-0.04367
O	3.39798	-0.39672	-0.60256
S	4.28046	0.61551	0.16596
C	5.63344	0.93675	-0.97092
H	6.40763	1.51684	-0.45565
H	6.03530	-0.02127	-1.32140
H	5.23745	1.51375	-1.81259
C	5.19248	-0.37055	1.36029
H	5.69685	-1.19694	0.84541
H	5.92106	0.27087	1.86994
H	4.47321	-0.75989	2.08936
C	-2.93823	-0.31605	-0.04142
C	-3.48416	-1.59928	-0.15407
C	-3.82911	0.75169	0.08838
C	-4.85682	-1.80814	-0.17074
H	-2.79849	-2.44065	-0.23853
C	-5.20704	0.55986	0.09795
C	-5.72096	-0.72413	-0.04423
H	-5.25283	-2.81658	-0.27518

H	-5.87003	1.41473	0.21643
H	-6.79918	-0.87285	-0.04783
C	-1.43925	-0.17451	-0.11556
Cl	-3.24662	2.39535	0.31097

***o*-Et CP3 M06**

O	-0.72296	0.48002	0.64421
O	-0.80270	-1.47420	-0.42197
Ag	1.33161	-0.85024	-0.10180
O	3.52274	-0.60817	-0.08998
S	4.07267	0.83469	-0.01384
C	5.46472	0.83683	-1.15139
H	6.00405	1.78618	-1.05201
H	6.12160	-0.00926	-0.91669
H	5.06875	0.74170	-2.16755
C	5.01408	0.87996	1.51716
H	5.69864	0.02370	1.54238
H	5.56977	1.82333	1.57108
H	4.30413	0.82296	2.34861
C	-2.86098	-0.42131	0.08281
C	-3.53225	-1.64726	0.11360
C	-3.59861	0.78288	0.03989
C	-4.91980	-1.71483	0.13012
H	-2.93659	-2.55830	0.12815
C	-4.99391	0.69022	0.03362
C	-5.65285	-0.53496	0.08825
H	-5.42246	-2.68021	0.16849
H	-5.59080	1.59942	-0.01502
H	-6.74191	-0.56233	0.09150
C	-1.35554	-0.45596	0.10680
C	-2.92476	2.13372	-0.02693
H	-2.41562	2.32066	0.92895
H	-2.10593	2.08168	-0.75838
C	-3.82598	3.30939	-0.36211
H	-4.34560	3.17034	-1.32049
H	-4.58870	3.48605	0.40837
H	-3.22905	4.22703	-0.44024

***o*-F CP3 M06**

O	-0.73911	1.03360	0.00000
O	1.47728	0.79265	0.00000
Ag	0.50433	-1.22622	0.00000
O	-0.01925	-3.36800	0.00000
S	-1.51824	-3.74457	0.00000
C	-1.68790	-4.91689	1.35325
H	-2.69918	-5.33961	1.33301
H	-0.93445	-5.70608	1.24446
H	-1.53613	-4.37322	2.29125
C	-1.68790	-4.91689	-1.35325
H	-0.93445	-5.70608	-1.24446
H	-2.69918	-5.33961	-1.33301
H	-1.53613	-4.37322	-2.29125
C	0.63089	2.99054	0.00000
C	1.93541	3.50033	0.00000
C	-0.40751	3.92610	0.00000
C	2.19355	4.86414	0.00000
H	2.75167	2.78161	0.00000
C	-0.17486	5.29456	0.00000
C	1.13161	5.76615	0.00000
H	3.22052	5.22459	0.00000
H	-1.02882	5.96907	0.00000
H	1.31713	6.83889	0.00000
C	0.41789	1.49966	0.00000
F	-1.68790	3.53965	0.00000

***o*-NH_2 CP3 M06**

O	-1.17338	1.20332	-0.08372
O	-0.93446	-1.00768	-0.10782
Ag	1.09142	-0.11001	-0.15842
O	3.18004	0.53960	-0.24810
S	4.30864	-0.38823	0.25587
C	5.19179	0.60425	1.46718
H	6.09554	0.06817	1.77971
H	5.44860	1.57131	1.01880
H	4.53259	0.74768	2.32935
C	5.54190	-0.31909	-1.04911

H	5.75360	0.73091	-1.28415
H	6.45054	-0.83185	-0.71268
H	5.13409	-0.83030	-1.92706
C	-3.13712	-0.15631	0.00228
C	-3.63712	-1.45724	0.14853
C	-4.99190	-1.72193	0.26789
H	-2.91260	-2.26885	0.17399
C	-5.42827	0.64681	0.09535
C	-5.88798	-0.64899	0.24408
H	-5.35012	-2.74339	0.38259
C	-1.65606	0.04204	-0.07211
C	-4.05299	0.92749	-0.03571
H	-6.95861	-0.82731	0.34337
H	-6.12881	1.48282	0.07157
N	-3.65380	2.22399	-0.24349
H	-4.29229	2.94451	0.07198
H	-2.66193	2.38646	-0.08428

_o_-NO_2 CP3 M06

O	0.64635	-0.40695	1.12173
O	0.79254	-0.38925	-1.11457
Ag	-1.36913	-0.31568	-0.57915
O	-3.56347	-0.30061	-0.54634
S	-4.30721	0.27501	0.68076
C	-5.53844	-0.97449	1.06986
H	-6.22108	-0.58281	1.83284
H	-6.08657	-1.23209	0.15571
H	-5.01513	-1.85381	1.45876
C	-5.42412	1.49891	-0.01626
H	-5.99090	1.03824	-0.83412
H	-6.09828	1.86055	0.76873
H	-4.82008	2.33016	-0.39376
C	2.78114	-0.55467	0.12605
C	3.27907	-1.85910	0.16974
C	3.71406	0.48468	0.16655
C	4.64320	-2.10759	0.24731
H	2.57486	-2.68991	0.14157
C	5.08668	0.25227	0.24524
C	5.55283	-1.05059	0.28573
H	5.00135	-3.13495	0.27794
H	5.76893	1.09694	0.27171
H	6.62159	-1.24269	0.34638
C	1.28112	-0.40042	0.05477
N	3.26557	1.87411	0.12206
O	4.11356	2.75686	0.15265
O	2.06322	2.08927	0.05577

***o*-OMe CP3 M06**

O	0.81397	0.62171	0.72298
O	0.75500	-1.05785	-0.75031
Ag	-1.31724	-0.33985	-0.50892
O	-3.42822	0.24967	-0.57466
S	-4.29738	0.14145	0.69885
C	-5.63345	-0.97101	0.24168
H	-6.37921	-0.98228	1.04502
H	-6.08047	-0.62717	-0.69867
H	-5.21002	-1.97309	0.11746
C	-5.24868	1.66659	0.70424
H	-5.71243	1.80064	-0.28047
H	-6.01205	1.61100	1.48899
H	-4.56149	2.49199	0.91544
C	2.84916	-0.47096	0.14944
C	3.32608	-1.76226	0.36295
C	3.77145	0.59199	0.07688
C	4.68190	-2.01810	0.55095
H	2.60381	-2.57715	0.39499
C	5.13445	0.33835	0.25303
C	5.57998	-0.95941	0.49682
H	5.03036	-3.03308	0.73343
H	5.85952	1.14642	0.19718
H	6.64590	-1.13498	0.63722
C	1.36396	-0.25756	0.03715
O	3.27289	1.81638	-0.20494
C	4.17376	2.89975	-0.28030
H	4.68898	3.06656	0.67687
H	4.92258	2.75581	-1.07304

H	3.57233	3.78178	-0.51823

***o*-OEt CP3 M06**

O	-0.63940	0.22481	0.76701
O	-0.59405	-1.32209	-0.84224
Ag	1.48725	-0.63714	-0.45506
O	3.66320	-0.33411	-0.47250
S	4.33240	0.53297	0.61763
C	5.23804	1.78203	-0.30417
H	5.87540	2.34810	0.38489
H	5.83995	1.28832	-1.07630
H	4.50811	2.45533	-0.76520
C	5.74609	-0.44605	1.14362
H	6.31056	-0.76004	0.25741
H	6.37379	0.15684	1.80996
H	5.36783	-1.32061	1.68262
C	-2.68588	-0.79755	0.10321
C	-3.17272	-2.10056	0.18473
C	-3.60012	0.27470	0.14218
C	-4.52987	-2.36531	0.34787
H	-2.45748	-2.92027	0.13021
C	-4.96538	0.01202	0.29250
C	-5.42031	-1.30027	0.40344
H	-4.88524	-3.39128	0.42553
H	-5.68509	0.82603	0.31971
H	-6.48749	-1.48130	0.52635
C	-1.19915	-0.58883	0.00773
O	-3.09492	1.51764	-0.01226
C	-3.98960	2.62218	0.00015
H	-4.73128	2.51197	-0.80763
H	-4.53989	2.64641	0.95455
C	-3.17072	3.87180	-0.18262
H	-2.62769	3.84761	-1.13564
H	-3.82189	4.75408	-0.18062
H	-2.43980	3.98201	0.62805

***o*-OH CP3 M06**

O	-0.74368	1.09467	0.00000
O	1.46144	0.78413	0.00000
Ag	0.53178	-1.23495	0.00000
O	-0.02940	-3.35813	0.00000
S	-1.53190	-3.72354	0.00000
C	-1.70816	-4.89415	1.35342
H	-2.72214	-5.31039	1.33353
H	-0.95981	-5.68808	1.24397
H	-1.55246	-4.35137	2.29127
C	-1.70816	-4.89415	-1.35342
H	-0.95981	-5.68808	-1.24397
H	-2.72214	-5.31039	-1.33353
H	-1.55246	-4.35137	-2.29127
C	0.65802	3.01071	0.00000
C	1.95517	3.53607	0.00000
C	2.18386	4.90300	0.00000
H	2.78669	2.83355	0.00000
C	-0.20509	5.28262	0.00000
C	1.09054	5.77393	0.00000
H	3.20018	5.29234	0.00000
C	0.44260	1.53576	0.00000
H	1.25270	6.85133	0.00000
C	-0.43883	3.90130	0.00000
H	-1.06450	5.95160	0.00000
O	-1.70816	3.47676	0.00000
H	-1.65082	2.48029	0.00000

***o*-O^{i}Pr CP3 M06**

O	1.22309	0.22844	0.71371
O	-0.13680	-0.56092	-0.87031
Ag	-0.69493	1.54715	-0.44236
O	-1.55038	3.56943	-0.27939
S	-0.58484	4.77623	-0.30523
C	-1.08150	5.77222	1.10742
H	-0.53651	6.72317	1.08371
H	-2.16383	5.94262	1.06513
H	-0.81767	5.22039	2.01556
C	-1.24293	5.84444	-1.59370
H	-2.30922	6.01911	-1.40675

H	-0.68798	6.78992	-1.59230
H	-1.10250	5.33810	-2.55422
C	1.55753	-1.99329	-0.02190
C	2.94982	-1.94524	-0.06096
C	0.90869	-3.24615	0.02895
C	3.72113	-3.10230	-0.09885
H	3.42564	-0.96522	-0.06917
C	1.68757	-4.40970	0.00524
C	3.07635	-4.33257	-0.06789
H	4.80699	-3.04260	-0.14535
H	1.22442	-5.38957	0.04810
H	3.65267	-5.25683	-0.09034
C	0.81937	-0.68200	-0.04066
O	-0.43541	-3.20446	0.13695
C	-1.28329	-4.35965	0.25489
H	-2.27289	-3.88592	0.32112
C	-1.06694	-5.12247	1.54788
H	-1.03858	-4.43171	2.40015
H	-1.90816	-5.81124	1.70062
H	-0.14734	-5.71891	1.55667
C	-1.28748	-5.22613	-0.99017
H	-0.38534	-5.83814	-1.10295
H	-2.14414	-5.91131	-0.94492
H	-1.39940	-4.60600	-1.88858

H CP3 M06

O	-1.11694	1.17405	-0.00018
O	-1.24599	-1.05515	-0.00039
Ag	0.90364	-0.52347	-0.00048
O	3.09265	-0.61535	-0.00004
S	3.94051	0.67630	0.00056
C	5.10137	0.44305	-1.35256
H	5.84150	1.25135	-1.33289
H	5.58950	-0.53262	-1.24109
H	4.53771	0.48163	-2.29022
C	5.10134	0.44194	1.35345
H	5.58957	-0.53359	1.24129
H	5.84136	1.25034	1.33450
H	4.53758	0.47964	2.29109
C	-3.26974	0.16537	0.00009
C	-4.02918	-1.00704	0.00042
C	-3.92370	1.40013	-0.00005
C	-5.41848	-0.94800	0.00064
H	-3.51636	-1.96650	0.00054
C	-5.31301	1.46176	0.00012
H	-3.32304	2.30794	-0.00030
C	-6.06311	0.28743	0.00046
H	-6.00195	-1.86782	0.00090
H	-5.81442	2.42880	-0.00007
H	-7.15123	0.33578	0.00060
C	-1.76670	0.10852	-0.00019

***o*-Br+*o*-NO_2 CP3 M06**

O	-0.12166	0.73291	0.68747
O	0.09028	-0.88380	-0.84884
Ag	-2.08863	-0.64403	-0.54103
O	-4.27844	-0.66301	-0.51084
S	-5.02627	-0.07737	0.70985
C	-6.26571	-1.31981	1.09405
H	-6.94988	-0.92442	1.85370
H	-6.81083	-1.57507	0.17748
H	-5.74846	-2.20148	1.48567
C	-6.13148	1.15079	0.00247
H	-6.69652	0.69136	-0.81726
H	-6.80784	1.51912	0.78245
H	-5.52014	1.97718	-0.37403
C	2.05517	0.05061	0.02599
C	2.75002	-1.15724	0.04865
C	2.80215	1.23187	0.09495
C	4.13021	-1.16345	0.17721
H	2.20149	-2.09152	-0.03002
C	4.19234	1.21557	0.19987
C	4.87056	0.00981	0.25435
H	4.74536	2.15067	0.23873
H	5.95186	-0.02170	0.34689
C	0.54722	-0.01102	-0.04379

Br	1.98534	2.93498	-0.01627
N	4.83052	-2.44541	0.21692
O	6.04672	-2.42748	0.34454
O	4.16529	-3.46687	0.11960

***o*-Cl+*o*-NO_2 CP3 M06**

O	0.12684	1.13199	0.82920
O	0.24462	-0.58084	-0.61119
Ag	-1.87300	-0.50345	-0.01007
O	-3.98482	-0.63072	0.55646
S	-5.05868	-0.09015	-0.41659
C	-5.75541	1.33827	0.42252
H	-6.63539	1.68433	-0.13233
H	-6.02701	1.05781	1.44714
H	-4.99420	2.12529	0.43313
C	-6.44588	-1.20799	-0.18356
H	-6.66111	-1.29025	0.88840
H	-7.31566	-0.81971	-0.72594
H	-6.16258	-2.18377	-0.59080
C	2.25102	0.47328	-0.00584
C	2.98835	-0.70866	0.01738
C	2.96267	1.67772	-0.06505
C	4.37378	-0.66659	0.01544
H	2.46893	-1.66214	0.04328
C	4.35634	1.71163	-0.09165
C	5.07685	0.53113	-0.03968
H	4.87257	2.66648	-0.15345
H	6.16260	0.53579	-0.04783
C	0.74584	0.36256	0.08169
Cl	2.13824	3.21101	-0.17153
N	5.12101	-1.92067	0.06388
O	6.34227	-1.85748	0.03802
O	4.48896	-2.96544	0.12983

***o*-F+*o*-NO_2 CP3 M06**

O	-1.23398	0.38698	0.00000
O	0.98464	0.13579	0.00000
Ag	0.03399	-1.89390	0.00000
O	-0.49494	-4.03086	0.00000
S	-1.99301	-4.41215	0.00000
C	-2.15816	-5.58477	1.35329
H	-3.16808	-6.01076	1.33350
H	-1.40220	-6.37153	1.24406
H	-2.00766	-5.04059	2.29119
C	-2.15816	-5.58477	-1.35329
H	-1.40220	-6.37153	-1.24406
H	-3.16808	-6.01076	-1.33350
H	-2.00766	-5.04059	-2.29119
C	0.14619	2.33266	0.00000
C	1.44930	2.82439	0.00000
C	-0.88645	3.27794	0.00000
C	1.68684	4.19068	0.00000
H	2.27321	2.11751	0.00000
C	-0.64988	4.64924	0.00000
C	0.64956	5.11972	0.00000
H	-1.49948	5.32765	0.00000
H	0.86111	6.18486	0.00000
C	-0.07478	0.83916	0.00000
F	-2.15816	2.89910	0.00000
N	3.06448	4.66860	0.00000
O	3.96292	3.83802	0.00000
O	3.25097	5.87828	0.00000

A.2.2. Cartesian geometries of TS structures at M06 level of computation.

***o*-Br TS M06**

O	-1.87148	-0.68495	-2.34937
O	-1.13538	-2.69351	-1.50508
Ag	0.72888	-0.60622	-0.34692
O	2.82672	-0.23281	-0.86582
S	3.77632	0.38767	0.17928
C	3.70431	-0.70421	1.60643
H	4.24976	-0.24583	2.43986
H	2.65208	-0.87132	1.87805
H	4.17945	-1.65132	1.33087
C	2.88513	1.77449	0.89892
H	1.92903	1.42520	1.31565
H	3.50192	2.22606	1.68529
H	2.70674	2.50743	0.10472
C	-1.38017	-0.72297	0.25246
C	-1.92582	0.54014	0.51547
C	-1.72737	-1.73512	1.16494
C	-2.77683	0.80317	1.58154
C	-2.56438	-1.50518	2.25369
H	-1.34775	-2.74100	0.98059
C	-3.09682	-0.23523	2.45437
H	-3.18096	1.80153	1.73985
H	-2.81218	-2.31629	2.93692
H	-3.76700	-0.04262	3.29075
C	-1.45327	-1.53932	-1.62257
Br	-1.46677	2.02952	-0.60386

***o*-CF_3 TS M06**

O	0.49443	0.21196	2.44786
O	-0.16857	-1.93905	1.97186
Ag	-0.65485	-0.51702	-0.64910
O	-2.65496	-0.09511	-1.44556
S	-3.75702	0.42078	-0.49865
C	-2.96982	1.63105	0.57525
H	-3.71107	2.00944	1.28972
H	-2.13036	1.16366	1.11061
H	-2.61258	2.45504	-0.05176
C	-3.98347	-0.86653	0.73697
H	-3.01629	-1.09378	1.20703
H	-4.70342	-0.51931	1.48778
H	-4.37847	-1.75353	0.23104
C	1.38323	-0.75830	0.13508
C	2.24810	0.32277	-0.12798
C	1.91091	-2.04264	-0.07384
C	3.56519	0.12722	-0.54432
C	3.21776	-2.25315	-0.50711
H	1.27879	-2.90170	0.15617
C	4.05101	-1.16252	-0.73415
H	4.21535	0.98250	-0.72816
H	3.59265	-3.26566	-0.65236
H	5.08017	-1.31155	-1.05622
C	0.29593	-0.83378	1.89969
C	1.83949	1.75679	0.06166
F	2.20973	2.50942	-0.99355
F	0.52389	1.95039	0.21370
F	2.43956	2.30181	1.13224

***o*-CH_3 TS M06**

O	-1.22000	1.78110	1.98509
O	-1.49470	2.74995	-0.08219
Ag	0.42627	0.38592	-0.46559
O	2.53367	0.49308	-1.06874
S	3.58732	-0.34789	-0.32077
C	2.94662	-2.02848	-0.30483
H	3.59469	-2.65887	0.31569
H	1.92146	-2.01851	0.09373
H	2.94760	-2.39882	-1.33521
C	3.34449	0.01178	1.42443
H	2.29305	-0.17132	1.68932
H	4.00638	-0.62572	2.02278
H	3.59808	1.06413	1.59044
C	-1.68534	0.05205	-0.05179
C	-1.95154	-1.04211	0.80531
C	-2.54424	0.25563	-1.14507
C	-3.05689	-1.86138	0.55620
C	-3.62985	-0.57785	-1.40194

H	-2.37133	1.12033	-1.78795
C	-3.88830	-1.63898	-0.53879
H	-3.26462	-2.69421	1.23087
H	-4.27951	-0.39192	-2.25688
H	-4.74360	-2.29165	-0.71184
C	-1.35979	1.95883	0.80870
C	-1.05190	-1.35768	1.96380
H	-1.56755	-1.95596	2.72715
H	-0.17499	-1.93844	1.63864
H	-0.68283	-0.43504	2.42875

***o*-Cl+*o*-Me TS M06**

O	0.04674	1.20040	2.12968
O	0.80194	-0.94262	2.36443
Ag	-0.52132	-0.13027	-0.58560
O	-2.54395	-0.46141	-1.36763
S	-3.76203	-0.11983	-0.48471
C	-3.50204	1.56895	0.07525
H	-4.29509	1.83838	0.78289
H	-2.51580	1.65018	0.55441
H	-3.55258	2.22398	-0.80092
C	-3.47448	-0.94097	1.08928
H	-2.48501	-0.65491	1.47508
H	-4.26083	-0.64890	1.79542
H	-3.51604	-2.02165	0.91787
C	1.52224	0.25771	0.17479
C	2.02191	1.56129	-0.08784
C	2.39715	-0.80245	-0.12334
C	3.33945	1.73752	-0.52449
C	3.70499	-0.64268	-0.55555
C	4.17974	0.65313	-0.73690
H	3.70659	2.74787	-0.70778
H	4.33294	-1.50642	-0.76527
H	5.20481	0.80976	-1.06930
C	0.57533	0.13961	1.88654
C	1.18079	2.79264	0.09222
H	1.55522	3.60180	-0.54834
H	1.20614	3.14459	1.13138
H	0.12767	2.61523	-0.15678
Cl	1.82811	-2.47525	-0.00481

***o*-NO_2+*o*-Me TS M06**

O	-0.18001	-1.41759	2.17065
O	-0.48542	0.85442	2.20055
Ag	0.57361	-0.28143	-0.66425
O	2.64037	-0.15992	-1.42612
S	3.77182	0.12088	-0.41673
C	3.64093	-1.17099	0.82817
H	4.32719	-0.94994	1.65434
H	2.60360	-1.21443	1.19173
H	3.91894	-2.12176	0.36175
C	3.19818	1.48583	0.60723
H	2.24506	1.21762	1.08621
H	3.95749	1.70463	1.36789
H	3.06643	2.35825	-0.04167
C	-1.49852	-0.36778	0.12829
C	-2.20703	-1.56868	-0.08351
C	-2.21397	0.81367	-0.11770
C	-3.55067	-1.52939	-0.48524
C	-3.54834	0.87591	-0.48339
C	-4.22019	-0.32810	-0.67344
H	-4.08006	-2.46902	-0.64844
H	-4.03773	1.83301	-0.64701
H	-5.26414	-0.32326	-0.98056
C	-0.47484	-0.29663	1.84672
C	-1.57261	-2.91253	0.12740
H	-1.99281	-3.64558	-0.57391
H	-1.76088	-3.28469	1.14375
H	-0.48618	-2.88282	-0.01115
N	-1.52538	2.11221	-0.00329
O	-0.37567	2.20768	-0.42265
O	-2.15496	3.05014	0.45761

***o*-CN TS M06**

O	0.76696	-0.53509	2.47139
O	1.08533	-2.48652	1.29176

Ag	-0.37919	-0.57539	-0.59880
O	-2.47965	-0.65449	-1.21406
S	-3.51188	0.18466	-0.43156
C	-2.89653	1.87400	-0.46255
H	-3.55051	2.50501	0.15153
H	-1.86708	1.90038	-0.07407
H	-2.92181	2.21999	-1.50109
C	-3.19995	-0.15031	1.30866
H	-2.14148	0.04463	1.53890
H	-3.84763	0.48973	1.92001
H	-3.43997	-1.20216	1.49768
C	1.70014	-0.23340	0.01690
C	1.96739	1.13902	0.24138
C	2.69127	-0.95297	-0.66088
C	3.15156	1.75282	-0.17929
C	3.87462	-0.35503	-1.09377
H	2.54206	-2.02134	-0.82243
C	4.10708	0.99564	-0.84832
H	3.31623	2.81183	0.01390
H	4.62596	-0.94676	-1.61508
H	5.03526	1.46138	-1.17378
C	0.99522	-1.33197	1.60594
C	0.97542	1.93786	0.89699
N	0.15466	2.59725	1.39570

***o*-CHO TS M06**

O	0.51101	-0.37180	2.39922
O	0.31624	-2.31328	1.18437
Ag	-0.36775	0.02255	-0.68240
O	-2.43431	0.28563	-1.40648
S	-3.59569	0.15918	-0.40176
C	-3.14165	1.17862	1.01092
H	-3.91432	1.08336	1.78361
H	-2.16534	0.85897	1.40318
H	-3.09217	2.21822	0.67007
C	-3.39127	-1.44265	0.39164
H	-2.37094	-1.52896	0.79301
H	-4.12883	-1.54181	1.19723
H	-3.56552	-2.21711	-0.36270
C	1.69708	-0.34175	0.01597
C	2.35409	0.89065	0.24485
C	2.47522	-1.37539	-0.51385
C	3.71987	1.05045	0.00044
C	3.83090	-1.20888	-0.80901
H	2.01651	-2.35566	-0.65311
C	4.45954	0.00328	-0.54277
H	4.19546	2.01008	0.21158
H	4.40299	-2.03741	-1.22580
H	5.52078	0.13093	-0.74945
C	0.55671	-1.18266	1.51622
C	1.62401	2.08159	0.70872
H	2.26388	2.86558	1.17254
O	0.42530	2.27286	0.58816

***o*-Cl TS M06**

O	0.64920	-0.27424	2.50353
O	0.60944	-2.32531	1.46662
Ag	-0.44342	-0.42256	-0.63372
O	-2.52563	-0.49434	-1.31181
S	-3.62862	0.10981	-0.41865
C	-3.15139	1.82360	-0.15553
H	-3.83350	2.28079	0.57121
H	-2.11618	1.85494	0.21441
H	-3.22884	2.34753	-1.11385
C	-3.29953	-0.47936	1.24921
H	-2.27690	-0.20368	1.54655
H	-4.02847	-0.03352	1.93680
H	-3.41509	-1.56828	1.24928
C	1.64314	-0.33630	0.05381
C	2.16658	0.96202	0.10139
C	2.50167	-1.30995	-0.48879
C	3.44744	1.29636	-0.31887
C	3.78426	-1.01156	-0.94002
H	2.15004	-2.34224	-0.51600
C	4.25939	0.29301	-0.84421
H	3.80574	2.32196	-0.24882

H	4.41904	-1.79520	-1.35112
H	5.26755	0.53923	-1.17381
C	0.74215	-1.15128	1.69251
Cl	1.16052	2.29022	0.70617

_o_-Et TS M06

O	1.13823	-0.22115	2.53676
O	1.33935	-2.34634	1.67667
Ag	-0.57583	-0.73432	-0.16057
O	-2.73516	-1.02772	-0.43587
S	-3.68059	0.18935	-0.44271
C	-2.92731	1.39373	-1.54650
H	-3.50730	2.32390	-1.51526
H	-1.88957	1.57564	-1.23068
H	-2.94733	0.98142	-2.56070
C	-3.36306	1.05901	1.09869
H	-2.28509	1.25849	1.18393
H	-3.93190	1.99655	1.10991
H	-3.69382	0.41785	1.92230
C	1.57019	-0.35916	-0.14297
C	1.92029	1.00565	-0.24235
C	2.34086	-1.29316	-0.85826
C	3.01421	1.38207	-1.03131
C	3.41904	-0.91200	-1.65024
H	2.10113	-2.35314	-0.75689
C	3.75632	0.43774	-1.73283
H	3.27983	2.43860	-1.10912
H	3.99928	-1.65864	-2.19210
H	4.60234	0.75471	-2.34232
C	1.24211	-1.15840	1.79933
C	1.14700	2.08282	0.47558
H	0.73825	2.78898	-0.26623
H	0.28492	1.62809	0.98362
C	1.98815	2.85167	1.48628
H	2.82811	3.36972	1.00326
H	1.38800	3.61144	2.00436
H	2.40044	2.17139	2.24284

_o_-F TS M06

O	-0.55893	1.27581	2.11103
O	-0.45737	2.57408	0.21378
Ag	0.36212	-0.33955	-0.54896
O	2.38865	-1.00511	-1.04911
S	3.58500	-0.45269	-0.24703
C	3.14766	-0.64123	1.48761
H	3.93179	-0.18543	2.10393
H	2.17999	-0.15324	1.67660
H	3.08317	-1.71223	1.70565
C	3.44128	1.33865	-0.31923
H	2.43710	1.63444	0.01741
H	4.20710	1.78619	0.32567
H	3.60247	1.65189	-1.35578
C	-1.68027	0.23597	-0.05459
C	-2.33446	-0.72876	0.71108
C	-2.45656	0.83177	-1.06488
C	-3.65915	-1.09812	0.53856
C	-3.78468	0.47907	-1.28808
H	-2.00283	1.62159	-1.66563
C	-4.38523	-0.48524	-0.47965
H	-4.10269	-1.85392	1.18445
H	-4.35670	0.96193	-2.07909
H	-5.42727	-0.76033	-0.63578
C	-0.64063	1.67050	0.98254
F	-1.64426	-1.35145	1.68782

_o_-NH_2 TS M06

O	-1.37203	1.94576	1.76402
O	-1.76079	2.71056	-0.37608
Ag	0.45675	0.44582	-0.44516
O	2.61219	0.70454	-0.76520
S	3.59966	-0.29807	-0.13626
C	3.06714	-1.92030	-0.70100
H	3.64404	-2.69451	-0.18094
H	1.99326	-2.03596	-0.49475
H	3.25487	-1.98306	-1.77778
C	3.09861	-0.47696	1.58240

H	2.04530	-0.78971	1.62791
H	3.74102	-1.22282	2.06567
H	3.22929	0.49391	2.07227
C	-1.63152	-0.00908	-0.12961
C	-1.90460	-0.95272	0.89255
C	-2.43980	-0.05094	-1.27820
C	-2.93776	-1.89128	0.73232
C	-3.45379	-0.98837	-1.45061
H	-2.27711	0.70113	-2.05320
C	-3.69291	-1.91250	-0.43200
H	-3.14013	-2.60407	1.53404
H	-4.05821	-0.99550	-2.35692
H	-4.48957	-2.64891	-0.53814
C	-1.54114	2.03553	0.58225
N	-1.12344	-0.97437	2.04340
H	-0.79110	-0.04454	2.29336
H	-1.56979	-1.42710	2.83666

_o_-NO_2 TS M06

O	0.45552	0.56362	2.27204
O	0.05229	-1.68930	2.03557
Ag	-0.51195	-0.34682	-0.69930
O	-2.58024	-0.13227	-1.42417
S	-3.69413	0.19125	-0.40813
C	-3.05345	1.51740	0.62581
H	-3.79759	1.76160	1.39356
H	-2.11098	1.20129	1.09604
H	-2.88773	2.39008	-0.01494
C	-3.62200	-1.11670	0.82377
H	-2.59088	-1.20909	1.19480
H	-4.30444	-0.87661	1.64768
H	-3.93655	-2.04990	0.34520
C	1.52606	-0.56214	0.13864
C	2.34273	0.54998	-0.09771
C	2.15522	-1.80406	-0.01679
C	3.68844	0.48174	-0.43376
C	3.49037	-1.91855	-0.40348
H	1.58516	-2.70537	0.21247
C	4.25913	-0.77518	-0.60614
H	3.94001	-2.90268	-0.52836
C	0.39966	-0.55560	1.84402
H	4.26724	1.38993	-0.58402
H	5.30572	-0.85711	-0.89216
N	1.76842	1.89979	0.02627
O	2.49944	2.79335	0.42516
O	0.59822	2.07693	-0.29648

_o_-OMe TS M06

O	0.56874	-0.10514	2.44323
O	0.39746	-2.24348	1.61616
Ag	-0.50417	-0.40038	-0.66086
O	-2.59106	-0.33691	-1.33097
S	-3.66809	0.24314	-0.39301
C	-3.05975	1.85636	0.12054
H	-3.74600	2.27823	0.86484
H	-2.05131	1.74797	0.54667
H	-3.03181	2.50360	-0.76238
C	-3.45030	-0.59863	1.18192
H	-2.41717	-0.46023	1.53151
H	-4.16008	-0.19037	1.91131
H	-3.65782	-1.66218	1.02289
C	1.56425	-0.46329	0.00330
C	2.16715	0.81599	0.02522
C	2.37017	-1.53784	-0.40009
C	3.51488	0.98885	-0.30578
C	3.70797	-1.38312	-0.75880
H	1.93242	-2.53735	-0.38260
C	4.27228	-0.11326	-0.70047
H	3.98177	1.97100	-0.27400
H	4.30642	-2.24205	-1.05959
H	5.32083	0.03292	-0.95884
C	0.60368	-1.06432	1.72683
O	1.36285	1.84662	0.37618
C	1.94012	3.12787	0.50991
H	2.31955	3.50694	-0.45050
H	1.14460	3.79086	0.86148

H	2.75720	3.12803	1.24570

***o*-OEt TS M06**

O	0.56680	0.25977	2.35942
O	-0.20278	-1.86699	1.94676
Ag	-0.60131	-0.35514	-0.67112
O	-2.58741	0.18145	-1.43220
S	-3.75115	0.38488	-0.44139
C	-3.13720	1.51670	0.81561
H	-3.90030	1.63821	1.59396
H	-2.20827	1.11764	1.24884
H	-2.94719	2.48227	0.33485
C	-3.79190	-1.09446	0.58121
H	-2.80369	-1.25445	1.03766
H	-4.55653	-0.97349	1.35800
H	-4.05445	-1.94073	-0.06230
C	1.38922	-0.81727	0.06636
C	2.29867	0.24851	-0.13129
C	1.89000	-2.11834	-0.08415
C	3.64414	0.00907	-0.42709
C	3.22184	-2.37715	-0.40389
H	1.21210	-2.95251	0.10532
C	4.09212	-1.30414	-0.56624
H	4.34657	0.82818	-0.56605
H	3.58119	-3.40014	-0.50750
H	5.14145	-1.48222	-0.80042
C	0.32284	-0.79051	1.83904
O	1.78100	1.49272	-0.02194
C	2.65716	2.61149	-0.04837
H	3.13666	2.69069	-1.03757
H	3.45479	2.47700	0.69956
C	1.83577	3.83552	0.25568
H	1.36370	3.74663	1.24223
H	2.47067	4.72965	0.25480
H	1.04647	3.97473	-0.49393

***o*-OH TS M06**

O	-0.51449	1.57650	1.92662
O	-0.94551	2.77974	0.00344
Ag	0.38049	-0.07790	-0.66750
O	2.44125	-0.45615	-1.30818
S	3.56842	-0.47487	-0.25588
C	3.00569	-1.57709	1.05000
H	3.73919	-1.57014	1.86511
H	2.02229	-1.24372	1.41437
H	2.93023	-2.58596	0.63090
C	3.41741	1.06427	0.66119
H	2.39325	1.16195	1.04833
H	4.14101	1.06028	1.48528
H	3.64382	1.88906	-0.02231
C	-1.68939	0.13667	-0.08613
C	-2.16637	-0.74847	0.89925
C	-2.56450	0.43996	-1.14465
C	-3.43605	-1.32782	0.81315
C	-3.82628	-0.13538	-1.25483
H	-2.24035	1.16056	-1.89875
C	-4.25227	-1.02980	-0.27024
H	-3.76806	-2.00310	1.60135
H	-4.47637	0.11001	-2.09373
H	-5.23971	-1.48563	-0.33824
C	-0.81681	1.92721	0.82063
O	-1.40900	-1.06997	1.97674
H	-0.72981	-0.37219	2.05510

***o*-O^{i}Pr TS M06**

O	0.35422	0.10159	2.25954
O	-0.27102	-2.09603	2.00726
Ag	-0.87352	-0.66219	-0.65613
O	-2.87771	-0.07633	-1.34069
S	-3.75879	0.76358	-0.39411
C	-2.69714	2.06546	0.25370
H	-3.27394	2.67887	0.95659
H	-1.82683	1.62140	0.75813
H	-2.37397	2.68296	-0.59147
C	-3.90142	-0.19556	1.12119
H	-2.89767	-0.48580	1.46408

H	-4.40685	0.40793	1.88454
H	-4.49771	-1.08736	0.90231
C	1.16149	-1.06289	-0.00930
C	2.00843	0.03888	-0.26784
C	1.71182	-2.34729	-0.13662
C	3.35522	-0.15448	-0.59591
C	3.04412	-2.55500	-0.48298
H	1.07880	-3.20586	0.09395
C	3.86023	-1.44823	-0.70255
H	4.01033	0.68815	-0.80404
H	3.44779	-3.56308	-0.56912
H	4.90877	-1.58568	-0.96582
C	0.16611	-0.99444	1.81260
O	1.40588	1.25375	-0.23600
C	2.05518	2.45903	0.21417
H	1.19420	3.07300	0.51777
C	2.75825	3.17868	-0.91962
H	2.09252	3.28466	-1.78543
H	3.04865	4.18566	-0.59090
H	3.66933	2.66088	-1.24511
C	2.92731	2.25441	1.43552
H	3.88594	1.77555	1.20203
H	3.14773	3.23316	1.88115
H	2.40047	1.64575	2.18023

H TS M06

O	0.51867	2.23893	-1.13017
O	0.62159	2.27515	1.17319
Ag	-0.24876	-0.58198	-0.00008
O	-2.26243	-1.45284	-0.03076
S	-3.51895	-0.56171	0.01140
C	-3.33423	0.60556	-1.34464
H	-4.08801	1.39596	-1.24572
H	-2.32245	1.03531	-1.30491
H	-3.48514	0.06959	-2.28700
C	-3.25876	0.60962	1.35048
H	-2.29391	1.11668	1.20649
H	-4.07822	1.33836	1.35156
H	-3.25891	0.05350	2.29378
C	1.79784	0.13428	0.00603
C	2.49818	-0.02958	-1.20103
C	2.49961	-0.11981	1.19762
C	3.82828	-0.44415	-1.22483
H	1.99473	0.20681	-2.14080
C	3.82945	-0.53415	1.18684
H	1.99890	0.03752	2.15535
C	4.49424	-0.70012	-0.02771
H	4.34987	-0.56017	-2.17506
H	4.35342	-0.72207	2.12423
H	5.53722	-1.01508	-0.03966
C	0.68949	1.96071	0.02138

***o*-Br+*m*-NO_2 TS M06**

O	-0.20683	1.23672	2.38324
O	-0.30217	-1.05887	2.30465
Ag	-1.01851	-0.15397	-0.50337
O	-2.96649	-0.40913	-1.47052
S	-4.16092	-0.93768	-0.64801
C	-4.24395	0.10111	0.81773
H	-4.98756	-0.31020	1.51100
H	-3.25347	0.13437	1.29543
H	-4.54754	1.10571	0.50569
C	-3.57362	-2.43126	0.16265
H	-2.67390	-2.19918	0.75040
H	-4.36473	-2.82080	0.81476
H	-3.34249	-3.16748	-0.61407
C	1.00648	0.10301	0.35048
C	1.66094	1.26029	-0.09561
C	1.76426	-1.07492	0.31929
C	2.98508	1.28181	-0.52917
C	3.07862	-1.06846	-0.12925
H	1.32446	-2.00039	0.68683
C	3.70809	0.09898	-0.54763
H	3.44855	2.20872	-0.85966
H	4.74301	0.08017	-0.87727
C	-0.10022	0.09653	2.03026

Br	0.72304	2.91674	-0.16153
N	3.83236	-2.32008	-0.14818
O	3.26884	-3.33590	0.23535
O	4.98803	-2.28771	-0.54880

***o*-Cl+*m*-NO_2 TS M06**

O	-0.44848	1.03708	2.38263
O	0.02179	-1.20543	2.20051
Ag	-0.88415	-0.33693	-0.57815
O	-2.83144	-0.87697	-1.43901
S	-4.11338	-0.63035	-0.61595
C	-3.94052	1.02034	0.07867
H	-4.80830	1.23622	0.71369
H	-3.01364	1.07571	0.66886
H	-3.90736	1.73326	-0.75235
C	-3.89218	-1.54640	0.91485
H	-2.93250	-1.26103	1.36891
H	-4.72142	-1.31612	1.59433
H	-3.89660	-2.61477	0.67566
C	1.02454	0.32294	0.32863
C	1.39690	1.62365	-0.04112
C	2.04013	-0.63962	0.25937
C	2.68812	1.98586	-0.41984
C	3.32450	-0.29843	-0.14459
H	1.82243	-1.66131	0.56464
C	3.66936	1.00872	-0.47320
H	2.92370	3.01539	-0.68005
H	4.68707	1.25377	-0.76318
C	-0.06246	-0.02461	1.98062
N	4.35214	-1.33455	-0.21253
O	4.03227	-2.48115	0.06967
O	5.48016	-1.00226	-0.55093
Cl	0.18977	2.90102	-0.06338

***o*-F+*m*-NO_2 TS M06**

O	0.19706	-2.06710	2.01976
O	0.21153	0.20483	2.38107
Ag	0.96711	-0.26801	-0.59522
O	2.93656	0.21921	-1.41874
S	3.98490	0.89495	-0.51081
C	4.11255	-0.14594	0.95038
H	4.78415	0.33116	1.67412
H	3.11445	-0.28695	1.39004
H	4.52999	-1.10964	0.64084
C	3.14087	2.28169	0.26288
H	2.22805	1.92309	0.76107
H	3.81487	2.74988	0.99031
H	2.88867	3.00199	-0.52219
C	-1.04080	-0.61489	0.23063
C	-1.66241	-1.73725	-0.32210
C	-1.84241	0.52644	0.33862
C	-2.99155	-1.78580	-0.72705
C	-3.16656	0.50988	-0.08634
H	-1.43392	1.42792	0.79164
C	-3.75782	-0.63860	-0.61114
H	-3.40471	-2.70620	-1.13359
H	-4.79960	-0.62689	-0.91826
C	0.05260	-0.88312	1.89386
N	-3.96805	1.72191	0.02963
O	-3.43558	2.72293	0.49139
O	-5.13312	1.68022	-0.34481
F	-0.93737	-2.84843	-0.48231

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Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3172

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COMMUNICATION

Selective deuteration of (hetero)aromatic compounds *via* deutero-decarboxylation of carboxylic acids†

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Received 19th January 2012, Accepted 1st March 2012
DOI: 10.1039/c2ob25157d

A practical, mild and highly selective protocol for the mono-deuteration of a variety of arenes and heteroarenes is presented. Catalytic amounts of Ag(I) salts in DMSO/D_2O are shown to facilitate the deutero-decarboxylation of *ortho*-substituted benzoic and heteroaromatic α-carboxylic acids in high yields with excellent levels of deuterium incorporation.

Synthetic procedures able to incorporate deuterium (D) and tritium (T) into organic molecules are highly sought after for a plethora of applications:[1] deuterium-labelled compounds are commonly used for mechanistic investigations of catalytic cycles and reaction pathways,[2] in stable-isotope tracer studies, as analytical standards,[3] in neutron scattering,[4] and for the synthesis of drug compounds with enhanced metabolic stability.[5] On the other hand, tritium is arguably the most versatile radionuclide available, with tritiated compounds regularly exploited as radiotracers in the pharmaceutical industry from drug discovery level to clinical studies.[1,6] Synthetic methods for the preparation of deuterated compounds are regularly applied towards the synthesis of their tritium-labelled isotopologues, and deuteration methodologies are commonly used as synthesis optimisation tools for subsequent tritium labelling.[1] Despite the high demand, methods for the selective incorporation of a single deuterium into an aromatic ring are scarce.[1,7,8] The most common protocol involves halogen/D exchange; this is usually mediated by strong bases, with the consequent limitation in functional group scope. H/D exchange reactions can also be employed with the use of strong acids,[9] bases,[10] or transition metal catalysts.[11] However,

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†Electronic supplementary information (ESI) available: Experimental procedures and characterisation of new compounds. See DOI: 10.1039/c2ob25157d

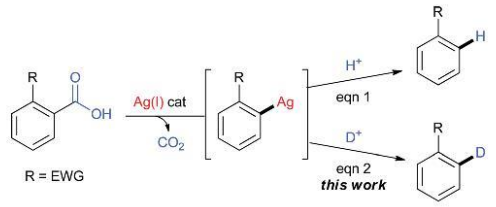
Table 1 Optimisation of the Ag(I)-catalysed deutero-decarboxylation[a]

R = H, **1a**
R = Na, **Na-1a**
R = K, **K-1a**

2a

Entry	Substrate	AgX	(Mol %)	D_2O (equiv.)	Solvent	Yield[b] (%)	D (%)[c]
1	**Na-1a**	$AgNO_3$	(20)	10	DMSO	35	87
2	**Na-1a**	AgOTFA	(20)	10	DMSO	20	92
3	**Na-1a**	AgOAc	(20)	10	DMF	61	85
4	**K-1a**	$AgNO_3$	(20)	10	DMF	39	77
5	**K-1a**	AgOTFA	(20)	10	DMF	30	70
6	**K-1a**	AgOAc	(20)	10	DMF	20	77
7	**1a**	Ag_2CO_3	(10)	0	DMSO	100	0
8	**1a**	Ag_2CO_3	(10)	10	DMSO	100	82
9	**1a**	**Ag_2CO_3**	**(10)**	**50**	**DMSO**	**92**	**92**
10	**1a**	Ag_2CO_3	(10)	100	DMSO	48	91

[a] Reaction conditions: the reactions were carried out using 1.0 equiv. of the substrate and the indicated amounts of Ag(I) catalyst and D_2O in a 0.2 M solution of the stated solvent. [b] The yield of **2a** was determined by ^1H NMR analysis using mesitylene as an internal standard. [c] The extent of deuteration of **2a** was determined by ^1H NMR analysis using mesitylene as an internal standard.



Scheme 1 Ag(I)-catalysed proto- and deutero-decarboxylations of benzoic acids (eqn (1) and (2), respectively).

these processes are generally non-selective, and only several examples are known where good selectivity is achieved.[12] Accordingly, there is a great need for the development of mild and selective methodologies for the incorporation of deuterium into aromatic rings.

Recently, we developed an operationally simple, high yielding proto-decarboxylation of *ortho*-substituted benzoic and hetero-aromatic α-carboxylic acids catalysed by Ag_2CO_3.[13,14] This process is believed to proceed *via* an aryl–Ag(I) intermediate that is subsequently protonated (Scheme 1, eqn (1)). We hypothesised that if this reaction was carried out in the presence of a D^+ source, it could lead to selective incorporation of deuterium (Scheme 1, eqn (2)).[15]

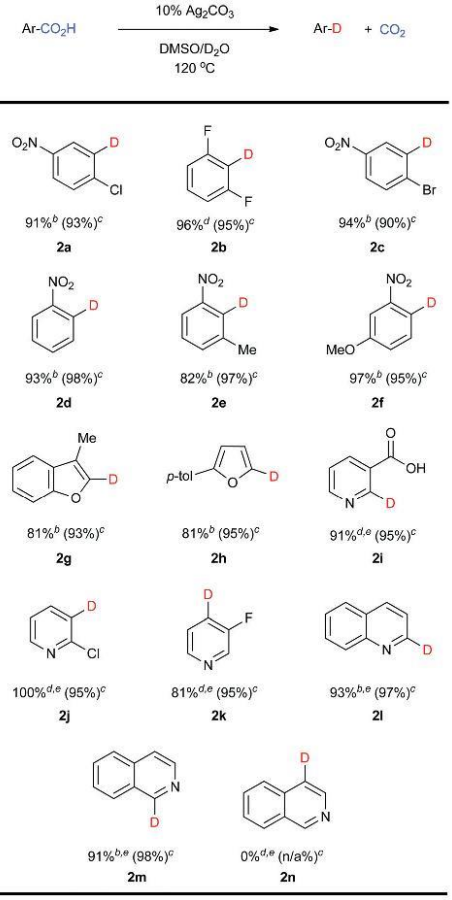
Initially, in order to completely avoid the presence of H^+ in the reaction, we tested the decarboxylation of K and Na salts of benzoic acid **1a** (Table 1, entries 1–6) with a variety of Ag(I) catalysts, in combination with 10 equiv. of D_2O.[16] Gratifyingly, good levels of deuterium incorporation were observed in the resulting arene **2a**, albeit in moderate to good yields. Pleasingly, direct decarboxylation of the carboxylic acid **1a** with Ag_2CO_3 afforded higher yields and a similarly good level of deuteration when carried out in the presence of 50 equiv. of D_2O (entries 7–10).

With this optimised protocol in hand, we examined the scope of the reaction (Table 2). The standard reaction conditions consistently afforded high yields (82–100%) and deuteration selectivities (91–99%) with a variety of substituted benzoic acids.

This methodology allows the synthesis of arenes deuterated *ortho* to a variety of electron-withdrawing substituents such as Cl (**2a**), F (**2b**), Br (**2c**) and NO_2 (**2d–f**) under very mild and practical conditions: the benzoic acid is simply mixed with the catalyst and 50 equiv. of D_2O, and heated up in DMSO. After the reaction, the residual amounts of starting material are easily removed during aqueous workup, affording high purity product after solvent evaporation, thus removing the need for column chromatography or distillation. Alternative routes to these substrates generally involve treatment of the corresponding *ortho*-halo arene with a strong alkyl-lithium base, followed by quench with D^+, and sometimes challenging purifications.[17]

This protocol can also be successfully applied to heteroaromatic carboxylic acids (Table 2, **2g–m**). Thus, furans and benzofurans, selectively deuterated at position 2, can be easily prepared. Similarly, it is possible to selectively deuterate pyridine at positions 2, 3 or 4 by judicious choice of the carboxylic acid starting material (**2i–k**). Finally, quinolines are also amenable for selective deuteration at the position α to the heteroatom (**2l–m**).

Table 2 Substrate scope for the deutero-decarboxylation of homo- and hetero-aromatic carboxylic acids[a]



[a] Reaction conditions: all the reactions were carried out with 10 mol% Ag_2CO_3, 1.0 equiv. of aromatic carboxylic acid (**1**) and 50 equiv. of D_2O in a 0.2 M DMSO solution at 120 °C for 16 h. [b] Yields of isolated analytically pure material. [c] Percentage of deuteration was determined by ^1H NMR analysis using mesitylene as an internal standard. [d] The yield was determined by ^1H NMR analysis using mesitylene as an internal standard. [e] The reaction was carried out at 140 °C.

Remarkably, this method is completely selective for the C bearing the carboxylic acid and no deuteration is observed at any other position, as determined by ^2H NMR, even for arenes bearing electron-donating MeO substituents (**2f**) and for the nucleophilic furan **2h**.

In conclusion, we have developed a mild and practical methodology for the Ag(I)-catalysed deutero-decarboxylation of a variety of aromatic acids, bearing the carboxyl motif *ortho* to a functional group or α to a heteroatom. The protocol is

chemoselective and compatible with a wide range of synthetically useful functionalities such as halogens and nitro groups. Moreover, it is high yielding and affords excellent levels of selective deuterium incorporation. It is envisaged that this methodology should be easily adapted towards the tritium-labelling of pharmaceutically interesting molecules to aid drug development and clinical studies.

During the preparation of this manuscript, a methodology describing silver and copper mediated decarboxylative deuterations was reported by Goossen.[18]

We gratefully acknowledge the European Research Council for a Starting Research Grant (to I.L.), Pfizer Limited and the Engineering and Physical Sciences Research Council for a CASE studentship (R.G.), QMUL for a studentship (J.C.) and Harold Toms for NMR analysis.

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DOI: 10.1002/chem.201402931

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Decarboxylation

The *ortho*-Substituent Effect on the Ag-Catalysed Decarboxylation of Benzoic Acids

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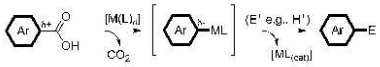
Abstract: A combined experimental and computational investigation on the Ag-catalysed decarboxylation of benzoic acids is reported herein. The present study demonstrates that a substituent at the *ortho* position exerts dual effects in the decarboxylation event. On one hand, *ortho*-substituted benzoic acids are inherently destabilised starting materials compared to their *meta*- and *para*-substituted counterparts. On the other hand, the presence of an *ortho*-electron-withdrawing group results in an additional stabilisation of the transition state. The combination of both effects results in an overall reduction of the activation energy barrier associated with the decarboxylation event. Furthermore, the Fujita–Nishioka linear free energy relationship model indicates that steric bulk of the substituent can also exert a negative effect by destabilising the transition state of decarboxylation.

Introduction

In the last decade, transition-metal-catalysed decarboxylative transformations have emerged as a powerful method for the formation of C–C bonds.[1] In particular, the use of bench-stable, readily available (hetero)aromatic carboxylic acids as aryl donors in cross-coupling reactions has found great utility, thus providing an efficient and green alternative to traditional methodologies.[2]

Traditionally, the decarboxylation mechanism has been believed to proceed through metal-mediated CO_2 extrusion with concomitant generation of an aryl-metal species, which can then undergo various transformations with a plethora of different electrophiles (Scheme 1). The simplest example is the coupling with H^+ in a protodecarboxylation reaction,[3] which has been demonstrated using Ag,[4,5] Cu,[6] Pd,[7,8] and Rh[9] catalysts,[10] the latter two being limited to bis-*ortho*-substituted electron-rich aromatic substrates.[11]



Scheme 1. General mechanism of transition-metal-catalysed protodecarboxylation.

Although Cu-catalysed systems have a broader scope and are applicable to *ortho*-, *meta*-, and *para*-substituted electron-deficient benzoic acids, high temperatures are required to assist decarboxylation.[6] Recently, we and others have demonstrated that Ag salts in coordinating solvents, such as DMSO or *N*-methylpyrrolidone (NMP), are very efficient at promoting decarboxylation of benzoic acids at temperatures 40–50 °C lower than those required in the Cu-catalysed system.[4,12] Under the standard conditions, the Ag-catalysed decarboxylations only proceed in the presence of an *ortho* substituent, which can be electron-withdrawing or electron-donating in nature.[4b] Further understanding of the nature of this *ortho*-effect would be of immense value, since it might permit the design of novel catalysts and prediction of the reactivities of unknown substrates.

Following an initial computational study by Gooßen and coworkers on the Ag/NMP and Cu/1,10-phenanthroline systems,[12] Lin and Su subsequently reported an elegant computational study on the mechanism of the Ag/DMSO decarboxylation system.[13,14] In this work, *ortho*, *meta*, and *para* regioisomers of several substituted benzoic acids are shown to have degenerate decarboxylation transition states. However, the *ortho* group causes an inherent steric destabilisation of the starting material, resulting in an overall reduction of the barrier to decarboxylation. Not surprisingly, in the case of *meta*- and *para*-substituted benzoic acids, no such steric effect is present, thus justifying their lack of reactivity.[4b] This led the authors to conclude that the *ortho*-effect is mainly steric in nature, and no

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403239.

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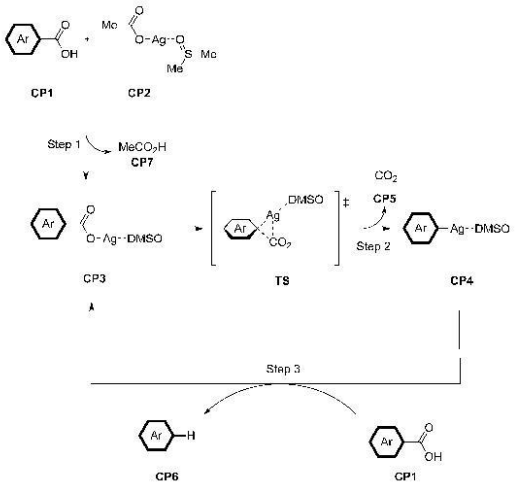
correlation was found with the electronic properties of the substituents. However, this was contrary to our findings with regard to the reactivity of substituents with different electronic properties. Therefore, we envisaged that a broader mechanistic understanding, including the effect of the electronic properties of *ortho* substituents, would be highly beneficial.

Herein, we present a combined computational and experimental mechanistic study on the effect of the *ortho* substituent in Ag-catalysed decarboxylation. Density functional theory (DFT) has been utilised to calculate the relative activation free energies of a variety of benzoic acids with substituents of different polarities and sizes. In addition, the initial rates of reaction of different carboxylic acids have been determined, thus allowing for direct comparison of the computational and experimental results. This synergistic study represents a step forward in the understanding of the factors that affect decarboxylation, and allows for the development of a quantifiable model of relative rates of decarboxylation for a given substrate based upon its polarity and/or steric bulk parameters.

Results and Discussion

Mechanism of the Ag-catalysed decarboxylation of substituted benzoic acids

As previously mentioned, our group has developed an Ag^{I}-catalysed decarboxylation of aromatic carboxylic acids in DMSO as solvent. The proposed catalytic cycle for this transformation is depicted in Scheme 2. The cycle is composed of three steps: step 1: initial ligand exchange through an acid-base reaction leading to the catalytically active species **CP3**; step 2: decarboxylation, which is rate-determining and therefore involves the most energetically demanding transition state (**TS**);[15] and step 3: regeneration of the catalyst by protodemetallation of aryl-Ag species **CP4** and formation of the product (**CP6**).



Scheme 2. Proposed mechanism for the Ag^{I}-catalysed decarboxylation of (hetero)aromatic acids.

The activation energy corresponds to the free energy of formation of the transition state (**TS**) from the Ag benzoate (**CP3**) (Scheme 2, step 2). For the Ag^{I}-catalysed decarboxylation of *ortho*-chlorobenzoic acid, the activation barrier is calculated to be 25.3 kcal mol^{-1}, which is comparable to the values calculated by Lin and Su.[13] Thermodynamically, the overall decarboxylation process for *ortho*-chlorobenzoic acid is exergonic ($\Delta G = -19.5$ kcal mol^{-1}), with both the initial ligand exchange (step 1) and the decarboxylation (step 2) having low energy requirements (-1.7 and -2.1 kcal mol^{-1}, respectively), and the catalyst regeneration being extremely exergonic (-15.7 kcal mol^{-1}).

The *ortho*-effect: a specific comparison of *ortho*-, *meta*-, and *para*-chlorobenzoic acids

In order to study the effect of substitution on the ring, the three isomers of chlorobenzoic acid were initially studied. Experimental results have demonstrated that in this system only *ortho*-chlorobenzoic acid undergoes decarboxylation, whereas the *meta* and *para* isomers, and benzoic acid itself, are unreactive (Table 1). This is supported by the present theoretical results for the four mentioned compounds: *ortho*-$ClC_6H_4CO_2H$ reacts with a much lower activation energy, $+25.3$ kcal mol^{-1}, compared to the other substrates ($+27.0$, $+28.1$, and $+28.4$ kcal mol^{-1}, respectively) (see Table 1).

Table 1. Comparison of the theoretical and experimental reactivities for Cl-C_6H_4-CO_2H.

	R	$\Delta G_X^{\ddagger}$ [kcal mol^{-1}][a]	$\Delta G_X^{\ddagger} - \Delta G_H^{\ddagger}$ [kcal mol^{-1}][a]	Conversion [%]
1	*ortho*-Cl	25.3	−3.0	37
2	*meta*-Cl	27.0	−1.4	0
3	*para*-Cl	28.1	−0.3	0
4	H	28.4	0	0

[a] $\Delta G^{\ddagger}$ calculated by DFT with the Becke–Perdew functional and TZP basis set (BP/TZP). [b] Reaction conditions: the benzoic acid (0.3 mmol) and Ag_2CO_3 (20 mol%) were heated to 120 °C in DMSO (0.2 M) for 16 h, conversion calculated by ^{1}H NMR using an internal standard.

A graphical representation of the reactivity difference between *ortho*- and *para*-chlorobenzoic acids is shown in Figure 1. Our calculations indicate that to reduce the activation barrier to decarboxylation, either the *ortho* **CP3** has to be destabilised or the *ortho* **TS** structure has to be stabilised. The *ortho* isomer is the least stable of the **CP3** structures, with a difference of $+3.0$ kcal mol^{-1} with respect to the *para* isomer; however, the corresponding transition state structures for both compounds are essentially degenerate ($+0.2$ kcal mol^{-1}). Therefore, since the *ortho* isomer starts from a more unstable structure but reaches a similarly energetic configuration in the transition state, this overall decrease in activation energy ($\Delta G^{\ddagger}_{ortho} = +25.3$ kcal mol^{-1} cf. $\Delta G^{\ddagger}_{para} = +28.1$ kcal mol^{-1}) implies an increased decarboxylation rate compared to the other chlorobenzoic acids.

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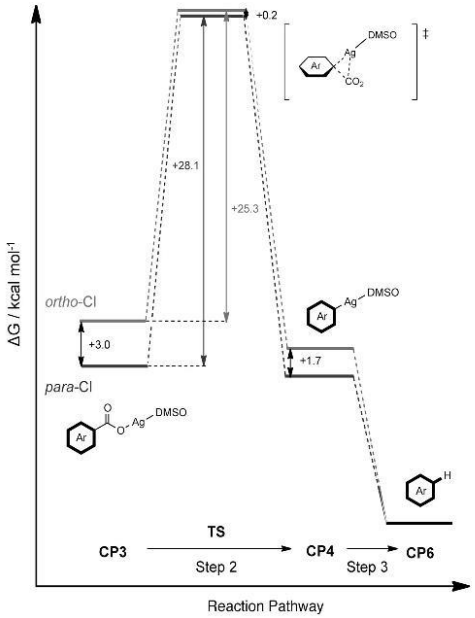

Figure 1. Archetypal energy profile for the decarboxylation of *ortho*- and *para*-chlorobenzoic acids. The reactivity of *ortho*-chlorobenzoic acid is exemplified by the destabilisation of the **CP3** substrate, leading to an overall reduction in the energy barrier to decarboxylation relative to the *para* compound.

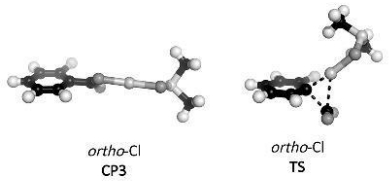

Figure 2. Geometries of the reactant (**CP3**) and the transition state (**TS**) of the decarboxylation step for *ortho*-chlorobenzoic acid. For a colour version of this figure, see Figure S10 in the Supporting Information.

Table 2. Comparison of the relative stabilities of **CP3** and **TS** structures for *ortho* and *para* isomers of several substituted benzoic acids versus the relative BP activation barriers for decarboxylation.[a]

	R[b]	CP3 $G_{ortho}-G_{para}$ [kcal mol^{-1}]	TS $G^{+}_{ortho}-G^{+}_{para}$ [kcal mol^{-1}]	$\Delta G^{+}_{ortho}-\Delta G^{+}_{para}$ [kcal mol^{-1}]	ΔG^{+}_{ortho} [kcal mol^{-1}]	Reactive isomer
1	CF_3	6.9	1.6	−5.3	25.3	*ortho*
2	NO_2	4.3	−0.8	−5.1	23.1	*ortho*
3	CHO	4.3	−0.4	−4.7	23.7	*ortho*
4	O*i*Pr	8.1	4.2	−3.9	24.6	*ortho*
5	Br	3.1	−0.2	−3.3	24.1	*ortho*
6	Et	3.3	2.1	−1.2	25.2	none
7	Cl	3.0	0.2	−2.8	25.3	*ortho*
8	Me	3.3	3.6	0.3	25.5	none
9	OEt	4.9	1.3	−3.6	25.0	*ortho*
10	CN	0.1	0.5	0.4	27.4	none
11	OMe	3.6	3.0	−0.6	26.4	*ortho*
12	NH_2	−0.9	0.7	1.6	26.5	none
13	OH	−7.2	−3.4	3.9	31.2	none
14	F	2.4	−0.1	−2.5	24.4	*ortho*

[a] Parameters calculated by DFT with the BP functional and TZP basis set. [b] Substituents ranked in order of decreasing substituent size (using Charton's epsilon parameters).[16]

The structural cause of the difference in **CP3**/**TS** stabilities among these isomers can be hypothesised in terms of the repulsive interaction between the *ortho* substituent and the carboxylic acid group in the **CP3** structure. Inherently, this proximity effect is significantly diminished in the **TS** structure and non-existent in the *meta* and *para* **CP3** substrates. This is illustrated by the increase in the average distance between the Cl atom and CO_2 moiety on going from the *ortho*-Cl **CP3** (3.52 Å) to the *ortho*-Cl **TS** (3.80 Å) as a consequence of steric relief (Figure 2). Similar steric effects that distinguish the reactivity of *ortho*, *meta*, and *para* isomers have previously been observed for Ag,[12,13] Cu,[12,13] and Pd[7]-mediated decarboxylation reactions.

The observed differentiation in reactivity among the three regioisomers of chlorobenzoic acid prompted us to carry out a deeper investigation into the factors that control decarboxylation in this system. Activation energies for fourteen different acids bearing electron-withdrawing and electron-donating substituents were computed with BP/TZP for each regioisomer (Table 2 (*ortho-para*), Table S2 (*ortho-meta*)). In most cases, a notable decrease in the activation barrier was observed for the *ortho* isomer (cf. *para*), the exceptions being those acids bearing Me, CN, NH_2, and OH substituents. Table 2 shows the relative stabilities of the **CP3** and the **TS** energies for different substrates, which allow us to assess the substituent effect on the **CP3** and **TS** in terms of the steric and electronic contributions.

Investigating the *ortho* effect on CP3

Similarly to the case of the chlorobenzoic acids, the increased reactivity of many of the *ortho* isomers results from the difference in relative stability of the **CP3** structures with respect to their *meta* and *para* isomers. For instance, the **CP3** structure of *ortho*-nitrobenzoic acid is 4.3 kcal mol^{-1} destabilised with respect to the *para* isomer, but the transition state is only marginally stabilised by 0.8 kcal mol^{-1}, resulting in an overall reduction in the activation energy by 5.1 kcal mol^{-1} (Table 2, entry 2). This energy difference is sufficient to make the decarboxylation feasible for the *ortho* compound ($\Delta G^{+}=+23.1$ kcal mol^{-1}), whereas the *para* compound remains completely unreactive ($\Delta G^{+}=+28.2$ kcal mol^{-1}).

In the case of *ortho*-O_2N-$C_6H_4CO_2H$, the substituent is one of the most sterically bulky groups and its sheer size impedes coplanarity of the NO_2 and COOH groups. Naturally, this steric hindrance is not present in the *meta* and *para* isomers (Figure 2). However, for the whole data set, only a rough corre-

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lation with the size of the substituent and the destabilisation of the **CP3** is observed, indicating that electronic effects might play an important role. For example, while substituent size decreases in the order $NO_2 > Me > OMe$, the **CP3** stabilisation energies decrease in the order $NO_2 > OMe > Me$.

It is worth mentioning that, in the case of OH and NH_2, the *ortho*/*para* reactivity is inverted. This is due to the fact that both groups can form hydrogen bonds between the substituent and the carboxylate unit, stabilising both the **CP3** and **TS** structures, and resulting in an overall increase in the barrier to decarboxylation.[13]

Investigating the *ortho*-effect on the TS

In order to analyse the electronic contribution of the *ortho* effect on the **TS**, similarly sized *ortho*-Br and *ortho*-Me (van der Waals radii of 1.85 and 1.97 Å (average), respectively)[17] were compared. The steric interactions in **CP3** lead to similar stabilisations (3.1 and 3.3 kcal mol^{-1}, Table 2, entries 5 and 8, respectively). However, these acids display remarkably different reactivities: after heating for 16 h under standard conditions, *ortho*-toluic acid showed no decarboxylation, whereas *ortho*-bromobenzoic acid reached 50% conversion. This disparity is associated with their significantly different electronic properties, as reflected in their **TS** energies: the electron-withdrawing *ortho*-Br substituent stabilises the transition state by -0.2 kcal mol^{-1}, whereas the weakly electron-donating *ortho*-Me substituent destabilises it by 3.6 kcal mol^{-1}, compared to the respective *para* isomers. This combination of both steric and electronic effects yields activation barriers of $+24.1$ kcal mol^{-1} for *ortho*-Br-$C_6H_4CO_2H$ and $+25.5$ kcal mol^{-1} for *ortho*-Me-$C_6H_4CO_2H$.

During the transition state, a build-up of electron density occurs at the *ipso* carbon atom during formation of the C(sp^2)-Ag bond and dissociation of the CO_2 fragment. The stabilising effect imparted by the electron-withdrawing Br atom is consistent with a reduction in the accumulating negative charge on the **TS** structure. In contrast, the inductively electron-donating Me group destabilises the transition state. To illustrate this concept, natural bond orbitals (NBO)[18] charges at the respective *ipso* carbon atoms of these compounds were calculated for the **TS** and **CP3** structures. Figure 3 shows that there is a significant correlation ($r = 0.78$) between the double difference NBO charges at the *ipso* carbon atom (*ortho*–*para* isomers) and the magnitude of $\Delta G^{+}_{ortho} - \Delta G^{+}_{para}$. This indicates that the electronic effect of the substituent has an overall effect on the activation energy and may not be limited to the stabilising influence on the **TS** structure. Comparable results are achieved using Mulliken charges (see Figure S2).

On the other hand, a destabilising steric effect on the **TS** is also observed for large substituents such as CF_3. Figure 3 shows that the relative NBO charges on the *ipso* carbon atoms are similar in the cases of *ortho*-CF_3 and *ortho*-Br, which is consistent with the electron-withdrawing nature of these substituents. However, this similarity is not observed in the **TS** energies, with the *ortho*-CF_3 group destabilising the **TS** with respect to the *para* isomer ($+1.6$ kcal mol^{-1}), indicating that the beneficial steric effect on **CP3** may be outweighed in the **TS**.[19]

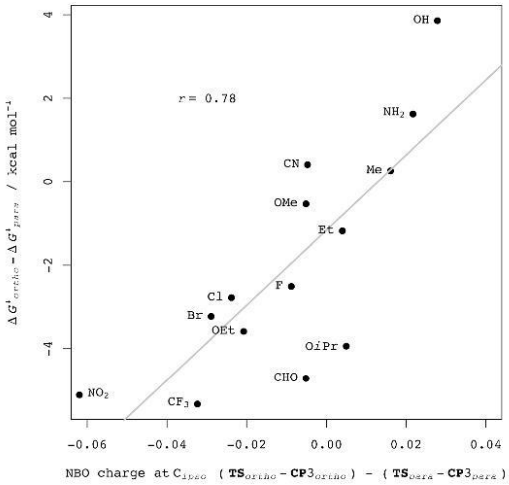

Figure 3. Correlation between $\Delta G^{+}_{ortho} - \Delta G^{+}_{para}$ and NBO charge double difference at C_{ipso} between the **TS** and **CP3** structures and also between the *ortho* and *para* compounds.

Theoretical and experimental agreement on the order of reactivity of *ortho* substituents

Having established that the influence of an *ortho* substituent on the Ag-catalysed decarboxylation of benzoic acids is a combination of steric and electronic factors, we set out to explore the influence of different substituents by comparing the activation energies calculated using the BP/TZP and M06/6-31G(d) methods and the experimental reaction rates for fourteen *ortho*-substituted benzoic acids (Table 3). In order to compare experimental and theoretical values, and to validate the computational procedure, the Eyring equation was used to derive the experimental activation energies with respect to *ortho*-F_3C-$C_6H_4CO_2H$. Overall, there is a moderate agreement between the experimental and theoretical relative activation energies ($r = 0.77$ for BP, Figure 4; $r = 0.63$ for M06, Figure S7, respectively).[20] The general trend in Table 3 shows that inductively electron-withdrawing substituents (e.g., *ortho*-NO_2, *ortho*-F, *ortho*-Cl, *ortho*-Br) tend to be more activating than electron-donating substituents (e.g., *ortho*-Me, *ortho*-OH, *ortho*-NH_2).

With these results in hand, we set out to quantify the extent to which electronic and steric parameters of a given substituent affect the rate of decarboxylation. Such study was deemed of great value, since it would allow for prediction of the reactivities of untested substrates by analysing these different properties.

Application of the Fujita–Nishioka equation, a linear free energy relationship

Linear free energy relationships (LFERs) have played an important role in determining the quantitative influence of substituents on various reactions. One of the earliest examples was the

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Table 3. Comparison of the theoretical and experimental activation energies ($\Delta G^{\ddagger}$) for a variety of benzoic acids.

	R[a]	Initial rate[b] [μmol min^{-1}]	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{CF_3}$ (exptl)[c] [kcal mol^{-1}]	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{CF_3}$ (calcd BP)[c,d] [kcal mol^{-1}]	$\Delta G^{\ddagger}_{X}-\Delta G^{\ddagger}_{o\text{-}CF_3}$ (calcd M06)[c,e] [kcal mol^{-1}]
1	*o*-NO_2	−53.0	−3.1	−2.2	−3.3
2	*o*-F	−18.7	−2.3	−0.8	0.6
3	*o*-Br	−7.92	−1.6	−1.2	−0.3
4	*o*-Cl	−6.35	−1.4	0.1	−0.4
5	*o*-OMe	−4.27	−1.3	1.1	−0.7
6	*o*-OEt	−4.25	−1.1	−0.2	−1.5
7	*o*-O*i*Pr	−4.01	−1.1	−0.7	−0.4
8	*o*-CF_3	−1.04	0.0	0.0	0.0
9	*o*-CN	unreactive	–	2.2	1.7
10	*o*-Me	unreactive	–	0.3	3.5
11	*o*-Et	unreactive	–	0.0	0.0
12	*o*-OH	unreactive	–	6.0	7.7
13	*o*-NH_2	unreactive	–	1.3	3.0
14	H	unreactive	–	3.1	4.5

[a] The compounds are ranked according to the energy of the experimentally calculated $\Delta G^{\ddagger}$ which was calculated using the Eyring equation; [b] Calculated using the initial rates method; [c] *ortho*-CF_3 used as a reference; [d] Energies calculated using BP/TZP. [e] Energies calculated using M06/6-31G(d).

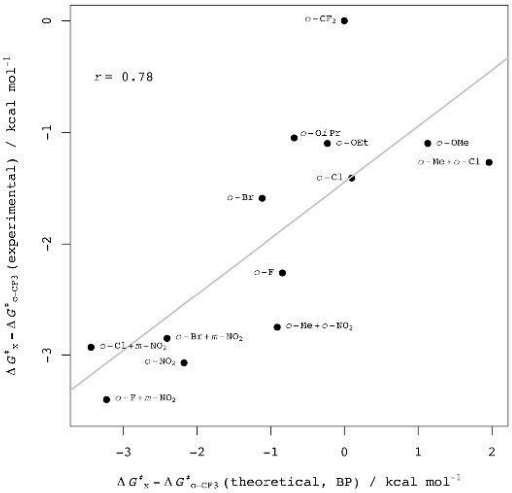

Figure 4. Statistically significant correlation between BP relative activation energy ($\Delta G^{\ddagger}_{BP}$) and experimental relative activation energy ($\Delta G^{\ddagger}_{exptl}$) for all thirteen tested compounds.

Hammett equation, which can be used to study the effect of a *meta* or *para* substituent on the rate of a reaction.[21] The Hammett equation cannot be used to analyse the effect of an *ortho* substituent as it only takes into account the ordinary polar effect of a substituent and neglects any additional steric or polar proximity effects. One of the most widely used relationships to account for the *ortho* effect was developed by Charton.[22] However, this LFER is only applicable to a contiguous set of mono-*ortho*-functionalised substrates and thus cannot be used to analyse a variety of mono- and disubstituted benzoic acids simultaneously.

Another widely used multi-parameter LFER was developed by Fujita and Nishioka.[23] This relationship can be used for comparison of *ortho*, *meta*, and *para* mono- or poly-substituted arenes by taking into account the separate polar and steric effects of a substituent [Eq. (1)].[24] In this relationship, the total polar effect is expressed in terms of the "ordinary" and "proximity" electrical effects using the pre-defined σ (Hammett) and *F* (Swain–Lupton–Hansch) parameters, respectively (in the case of *ortho* substituents $\sigma_o=\sigma_p$).[25] The steric contribution E_s^c is simply derived from the van der Waals radius of a group, with the critical assumption that any steric effect is primary in nature, resulting from the space-filling bulk of the group.[25]

$$\ln k_{o,m,p} = \rho\sigma_{o,m,p} + \delta E_s^{c,ortho} + fF_{ortho} + c \quad (1)$$

Steric and electronic parameters for all thirteen acids studied experimentally were compiled (Table 4),[24] and the susceptibility constants ρ, δ, and f were determined through multiple linear regressions (Table 5). Good correlations were found with both the experimental (Figure 5, $r=0.89$) and theoretical reactivity data (Figure 6 for BP, $r=0.91$).

Direct comparison of the susceptibility constants in Table 5 indicates that all three data sets are consistent in terms of the significance of the parameters, as indicated by the signs of the constants. The experimental and M06 theoretical data produce constants of similar magnitude, while the BP theoretical data produce slightly different constants albeit with the same implication and an excellent correlation to the model. The signs of the parameters indicate that polar effects ($\rho\sigma$ and f*F*) induce a rate enhancement, while an overall negative δE_s suggests

Table 4. Data correlation of the theoretical and experimental reaction rates for all benzoic acids tested using the Fujita–Nishioka equation.

	R[a]	$\ln(k_X/k_{CF_3})$ (exptl)	$\ln(k_X/k_{CF_3})$ (calcd)[b]	σ[c,d,e]	E_s[d,e]	F[d,e]
1	*o*-F + *m*-NO_2	4.35	4.13	0.77	−0.46	0.43
2	*o*-NO_2	3.93	2.79	0.76	−1.01[f]	0.67
3	*o*-Cl + *m*-NO_2	3.76	4.40	0.94	−0.97	0.43
4	*o*-Br + *m*-NO_2	3.66	3.08	0.94	−1.16	0.44
5	*o*-Me + *o*-NO_2	3.52	1.16	0.59	−2.25	0.63
6	*o*-F	2.89	1.08	0.06	−0.46	0.43
7	*o*-Br	2.03	1.43	0.23	−1.16	0.44
8	*o*-Cl	1.81	−0.13	0.23	−0.97	0.41
9	*o*-Cl + *o*-Me	1.63	−2.51	0.06	−2.21	0.37
10	*o*-OEt	1.41	0.29	−0.24	−0.55	0.26
11	*o*-OMe	1.41	−1.45	−0.27	−0.55	0.22
12	*o*-O*i*Pr	1.35	0.87	−0.45	−0.55	0.30
13	*o*-CF_3	0.00	0.00	0.54	−2.40	0.38

[a] The compounds are ranked according to the logarithmic experimentally calculated relative rate. [b] Derived by applying the Eyring equation at 120 °C to the data calculated using BP/TZP. [c] Assuming $\sigma_o=\sigma_p$, σ values. [d] From refs. [23,24]. [e] Parameters for disubstituted acids were calculated additively; see ref. [26] for precedent. [f] From the minimum perpendicular dimension of the NO_2 group.

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Table 5. Multi-linear regression analysis of the Fujita–Nishioka model for the experimental and theoretical relative rates of decarboxylation for the thirteen acids detailed in Table 4.[b]

Data set	*r*	c	ρ	δ	f
exptl	0.89	0.99	1.37	1.05	5.28
calcd (BP)	0.91	1.41	3.59	1.71	1.32
calcd (M06)	0.73[a]	−0.41	1.67	1.37	6.32

[a] All models are statistically significant at a *p* value of 0.01, except M06, which yields a *p* value of 0.066.

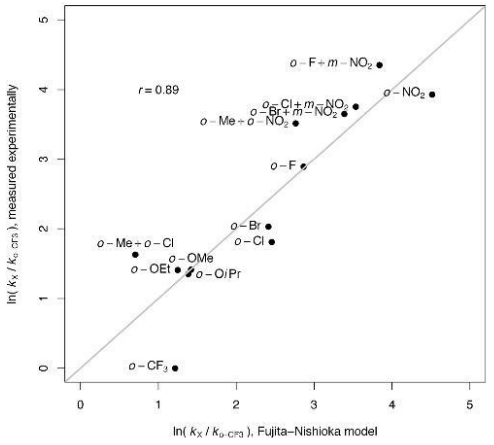

Figure 5. Plot of experimental logarithmic relative rates against the modified Fujita–Nishioka relationship [Eq. (1)].

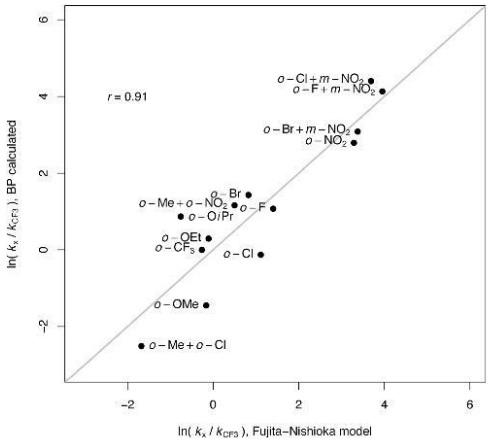

Figure 6. Plot of BP theoretical logarithmic relative rates against the modified Fujita–Nishioka relationship [Eq. (1)].

that bulky groups retard the reaction rate. In terms of the factors determining the *ortho* effect (f*F* and δE_s), it can be understood that a combination of low steric and high "proximity" polar effects is most important for promoting the decarboxylation of *ortho*-substituted benzoic acids.

The case of *ortho*-CF_3 (Table 4, entry 13) exemplifies the ambivalent behaviour of the steric factor. As discussed previously, the large and electron-withdrawing CF_3 greatly destabilises the starting structure **CP3** of the *ortho* isomer compared to the *para* isomer (+ 6.9 kcal mol^{-1}). However, the electron-withdrawing nature of this substituent fails to stabilise the transition state structure as any beneficial electronic effect seems to be offset by negative steric influence. This results in a **TS** destabilisation of + 1.6 kcal mol^{-1} (*ortho-para*), an absolute activation barrier of 25.2 kcal mol^{-1}, and the lowest relative rate among the substrates tested in this study. Unfortunately, the dichotomy of the steric effects in this system cannot be easily accounted for by the Fujita–Nishioka model as one set of steric parameters is defined for the reaction as a whole. Nevertheless, it is evident here that steric effects can have opposing contributions on the **CP3** and **TS** structures.

To probe the effect of further substitution on the ring, we investigated the *ortho*-halogen series (F, Cl, Br) with the addition of an NO_2 group at a position *meta* to the carboxylic acid. The overall "ordinary" polar coefficient (σ) of the two substituents was calculated by addition of the individual parameters (Table 4, entries 1, 3, and 4). A good correlation was obtained for all three models, with an increased activation towards decarboxylation upon appending an electron-withdrawing group at a *meta* position, which is consistent with the positive $\rho\sigma$ term.

Next, the effect of a second substituent at the other *ortho* position was investigated. Experimental and theoretical relative rate data for *ortho*-Cl + *ortho*-Me-$C_6H_3CO_2H$ were obtained (Table 4, entry 9). Incorporation of a methyl group, which is both weakly electron-donating and sterically demanding, resulted in a decrease in the rate of decarboxylation compared to the mono *ortho*-Cl-$C_6H_4CO_2H$, as reflected in both the experimental and theoretical data (Table 4, entry 8). Analysis of the polar and steric parameters for this acid revealed a significant increase in the steric parameter (E_s from −0.97 to −2.21) and slight reductions in both polar components (σ from 0.23 to 0.06; *F* from 0.41 to 0.37). Moreover, a similar decrease in reactivity was also observed in the case of *ortho*-Me + *ortho*-O_2N-$C_6H_3CO_2H$ (Table 4, entry 5). This additional *ortho*-Me group again resulted in a decrease in the experimental and theoretically calculated relative rates ($\ln k_{rel}$ (exptl) from 3.93 to 3.52 and $\ln k_{rel}$ (calcd) from 2.79 to 1.17, Table 4, cf. entries 2 and 5).

Conclusion

We have presented an exhaustive mechanistic study on the Ag-catalysed decarboxylation of *ortho*-substituted benzoic acids, which combines experimental and computational approaches, as well as use of the Fujita–Nishioka linear free energy relationship model. These studies have demonstrated that *ortho* substituents lead to a much lower activation energy

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barrier for decarboxylation compared to their *meta* and *para* counterparts due to a combination of steric and electronic effects. In particular, a sterically driven destabilisation of the **CP3** intermediate combined with a stabilisation of the **TS** by electron-withdrawing substituents and an additional steric destabilisation of the **TS** are the major factors in governing reactivity.

These results are in contrast to previous studies by Lin and Su, which suggested only a steric effect on the rate of decarboxylation. Our combined computational and kinetic studies have allowed us to clearly delineate both a steric contribution (a beneficial sterically driven destabilisation of the **CP3** intermediate and an opposing additional destabilisation of the TS for larger substituents) and an electronic contribution (a beneficial stabilisation of the TS by electron-withdrawing substituents) as the major factors in governing reactivity.

Experimental Section

Computational methods

The geometry optimisations and transition state (**TS**) calculations were carried out mainly with the ADF2009 program using DFT.[27] The local density approximation (LDA), characterised by electron-gas exchange, was used together with the Vosko–Wilk–Nusair (VWN) parameterisation for correlation. Gradients were corrected by means of Becke and Perdew (BP) non-local corrections to the exchange and correlation energies, respectively. Triple-ζ and polarisation (TZP) Slater basis sets were used to describe the valence electrons of all atoms. The inner core shells of C(1s), O(1s), N(1s), F(1s), Ag (1s-3d), Cl (1s-2p), Br (1s-3p), and S (1s-2p) were treated by the frozen core approximation. The ZORA formalism, implemented in DIRAC, with corrected core potentials was used to make relativistic corrections.[28] This is especially important for heavy atoms such as Ag. Default self-consistent field (SCF) and geometry optimisation convergence criteria were used.

Solvation effects were taken into account with the conductor-like screening model (COSMO) approach,[29] in which the solute molecule is embedded in a molecular-shaped cavity surrounded by a dielectric medium of a given dielectric constant ε; in the present case 46.7 for DMSO as solvent. Frequency calculations were also performed to identify all stationary points as minima (no imaginary frequency) or a **TS** (only one imaginary frequency) as well as to derive thermal enthalpy and entropy corrections, ultimately allowing us to calculate reaction free energies (ΔG_R) and activation free energies ($\Delta G^{\ddagger}$) at the standard state of 298.15 K and 1 M.

Additional calculations were carried out to assess the accuracy of the BP/TZP calculations from the previous section in the case of compounds with an *ortho* substituent. These extra calculations were performed with the Gaussian 09 package,[30] following the same procedure as previously, but with use of the recent M06 functional developed by Truhlar.[31] This functional has demonstrated good accuracy for the study of organometallic thermochemistry and kinetics. The standard 6-31G(d) basis set was used for light atoms, whereas the LANL2DZ effective core potential (ECP) was used for Ag. Solvation energies were also included by means of the self-consistent reaction field (SCRF) method based on the polarizable continuum model (PCM), with radii and non-electrostatic terms derived by Truhlar and co-workers.[32] Natural bond orbitals (NBO) analysis was performed as implemented in NBO version 3.1 within Gaussian 09.[33] All statistical analyses were performed with the R statistical package[34] at the 1% level of significance ($p < 0.01$) unless otherwise stated.

General procedure for the Ag-catalysed decarboxylation of benzoic acids

A mixture of benzoic acid (1.0 mmol) and Ag_2CO_3 (27.6 mg, 0.01 mmol) in anhydrous DMSO (5.0 mL) was stirred at 120 °C in a sealed vessel. At regular time intervals, aliquots (100 μL, 0.2 M, 0.02 mmol) of the solution were removed and quenched in a solution of the internal standard (mesitylene or trimethoxybenzene) in $CDCl_3$ (0.5 mL, 0.013 M, 6.7×10^{-3} mmol, $^1/_3$ equiv.). The absolute concentration of unreacted starting material was calculated by determining the relative ratio of unreacted starting material to product by integration of the product and starting material peaks in the ^{1}H NMR spectrum. The standard was added as an internal reference as the residual $CHCl_3$ peak could be shifted to $\delta = 8.32$ ppm in the presence of DMSO.

Calculation of initial rates and composition of the LFER model

For each substrate, several aliquots were taken at regular time intervals, ensuring that the conversion did not exceed 15%. For each of these aliquots, the absolute concentration of unreacted starting material was determined by ^{1}H NMR and plotted against time; the gradient was then calculated to give the initial rate for the given substrate. For each substrate, the relative rate was calculated using *ortho*-F_3C-$C_6H_4CO_2H$ as a reference compound and tabulated against the individual parameters of the Fujita–Nishioka relationship [Eq. (1)]. Least-squares regression analysis was used to calculate the susceptibility constants, which were then multiplied by their respective pre-defined parameters, combined, and plotted against the logarithmic relative rate to give the LFER shown in Figure 5.

Acknowledgements

We gratefully acknowledge the European Research Council for a Starting Research Grant (to I.L.), Pfizer Limited, the Engineering and Physical Sciences Research Council for a CASE studentship (R.G.), and QMUL for a studentship (J.C.). This work was also supported by the DGICYT-Spain (SAF2011–27642) and the Generalitat de Catalunya (2009SGR249). J.M.C. thanks Prof. F. Javier Luque of the Departament de Fisicoquímica of UB for his valuable suggestions and comments on the calculation section.

Keywords: catalysis · decarboxylation · density functional calculations · kinetics · linear free energy relationships

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[15] Kozlowski et al. have recently reported a combined experimental and theoretical study on Pd-catalysed decarboxylation (see ref. [8b]), from which they concluded that the rate-determining step can be either the decarboxylation or the protodemetallation, depending on the substrate. The Pd-catalysed protodecarboxylation regularly requires an exogenous proton/hydride source for catalyst regeneration, whereas this is not required in the Ag-catalysed system. The aryl-Ag intermediate is very nucleophilic and readily undergoes protodemetallation, thus supporting the inference that the decarboxylation is the rate-determining step in the Ag-catalysed protodecarboxylation.
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Received: April 3, 2014
Published online on October 21, 2014

